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A Neuroimaging Investigation into Hallucination Proneness in a Healthy Population

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By

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Declaration

The work presented in this thesis is the result of my own work. The material contained in this thesis has not been presented, nor is currently being presented, either wholly or in part, for any other degree or qualification.

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Abstract

The experience of hallucinations is one of the symptoms used in the diagnosis of a psychiatric disorders such as schizophrenia. Functional and structural neuroimaging studies consistently link hallucinatory experience with abnormalities in brain areas supporting normal processing such language areas in auditory verbal hallucinations (AVH) and visual sensory areas in visual hallucinations (VH).

Hallucinations are not confined to clinical populations, but are also relatively frequent in the general population. Finding that healthy individuals experience hallucinations without distress has led to models proposing that hallucinatory experiences lie on a continuum, which spans healthy and clinical populations.

Continuum models (e.g., Baumeister et al., 2017) provide a theoretical framework with testable hypotheses, that predict brain functional activation, morphometrics or microstructural alterations in the healthy hallucinator group from existing data in the clinical group. Healthy hallucinators therefore may be a key resource in informing transdiagnostic research into the neurological cause of hallucinations.

The aim of the current study is to test whether hallucination proneness predict a wide range of multi-modal neuroimaging measures in a large, healthy population. The Launay-Slade Hallucination Scale modified by Morrison's et al. (2000) $LSHS_{(M)}$ scale as well as auditory ($LSHS_{(A)}$) and visual ($LSHS_{(V)}$) subscales were used as a regressors in structural (VBM and FreeSurfer based morphometrics), functional (fMRI) and microstructural (DTI diffusivity and tractography) neuroimaging experiments to test whether alterations seen in patients translate into the healthy population.

The morphometric analysis of structural data showed a significant positive correlation between brain thickness in the temporal cortex (bilateral transverse temporal gyrus) (TTG) and $LSHS_{(M)}$ scores. Functional activation data shows a significant positive correlation between $LSHS_{(A)}$ scores and activation in irrelevant task activation (audio/visual) in right (inferior frontal gyrus, superior temporal gyrus and middle temporal gyrus). DTI diffusivity analysis showed that reduced mean diffusivity (MD) in the right inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF) and occipital lobe (OL), also reduced axial diffusivity (AD) in the bilateral (SLF) and (OL) were linked to higher $LSHS_{(M)}$ scores. The arcuate fasciculus

(AF) analysis showed that reduced diffusivity in the left (MD) and left (AD) were linked to high $LSHS_{(M)}$ scores.

It is striking that, for this healthy population, the effects observed are the opposite of what might have been expected (continuum theory) for brain pathology and contrasts with previously published data for schizophrenia patients suffering from hallucinations.

Finding consistent results using multiple imaging modalities in overlapping brain areas and for a relatively large population makes methodological differences or sampling effects an unlikely explanation for the results.

The continuum hypothesis of hallucination assumes that psychotic symptoms, such as AVH and VH, which are experienced in clinical and non-clinical populations, have a common cause. In neuroimaging terms this means that similar functional, structural, and microstructural parameters would be expected for clinical and non-clinical populations show the same direction of differences. Our data does not fit well with this model. However, the results failed to prove that.

Studying hallucinatory experiences in a healthy population is attractive because it avoids confounding effects, ranging from childhood trauma, medication or hospitalization. Our data suggests that studies in healthy individuals may not provide data that easily extrapolates to the causes underlying schizophrenic hallucinations.

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List of abbreviations

A	Axial diffusivity
AF	Arcuate fasciculus
AH	Auditory hallucination
ALIC	Anterior limb of the internal capsules
ANTs	Advance normalisation tools
AVH	Auditory verbal hallucination
BOLD	Bold oxygen level dependent
CAT12	Computational anatomy toolbox 12
CBF	Cerebral blood flow
CC	Corpus callosum
CNS	Central nervous system
CST	Cortico spinal tract
CVH	Clinical voice-hearers
DES	Dissociation experiences scale
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
Factor analysis	It is reducing the number of variables to explain and to interpret the results
FEW	Family-wise error
FFA	Fusiform Face Area
fMRI	Functional magnetic resonance imaging
FOF	Fronto-occipital fasciculus
GCA	Gaussian Classifier Atlas, it is used to label subcortical cortex
GLM	General linear models
GM	Grey matter
HC	Health controls
HC-HR	Healthy but high genetic risk
HVH	Health voice-hearers
IAT	Interhemispheric auditory tract
IFOF	Inferior frontal occipital fasciculus
ILF	Inferior longitudinal fasciculus

IOL	Inferior occipital lobe
IP	Inferior parietal
IPL	Inferior parietal lobe
IT	Inferior temporal
ITG	Inferior temporal gyrus
ITG	Inferior temporal gyrus
Kaiser criterion	It is dimensionality assessment based on eigenvalues of correlation matrix
lh	Left hemisphere
LI	Laterality index
LiMRIC	Liverpool magnetic resonance imaging Centre
LO	Lateral occipital
LOG	Lateral occipital gyrus
LSHS	Launay-Slade hallucination scale
LSHS-R	Launay-Slade hallucination scale revised
$LSHS_{(A)}$	Auditory subscale scores of LSHS
$LSHS_{(M)}$	Launay-Slade hallucination scale
$LSHS_{(V)}$	Visual subscale scores of LSHS
MD	Mean diffusivity
MNI	Montreal neurological institute
MOG	Middle occipital gyrus
MPRAGE	magnetisation-prepared radio-frequency pulses and rapid gradient-echo
MRI	Magnetic resonance imaging
MT	Middle temporal
MTG	Middle temporal gyrus
OM	Occipital middle
PaDS	Persecution and deservedness scale
PANSS	Positive and negative syndrome scale
Parc	Parcellation
PHG	Parahippocampal gyrus
RD	Radial diffusivity
rh	Right hemisphere

rMFG	Right middle frontal gyrus
SLF	Superior longitudinal fasciculus
SP	Superior parietal
SPM	Statistical parametric mapping
STG	Superior temporal gyrus
STG_A	Superior temporal gyrus anterior
STG_P	Superior temporal gyrus posterior
SZ-H	Schizophrenia patients with hallucinations
SZ-NH	Schizophrenia patients without hallucinations
Talairach registration.	It is coordinates as seed point use to transform the orig volume to the MNI305 atlas.
TBSS	Tract-based spatial statistic
TIV	Total intracranial volume
TPMs	Tissue probability maps
TT	Transverse temporal
UF	Uncinate fasciculus
VBM	Voxel-based morphometry
VH	Visual hallucination
VOTC	Ventral occipito-temporal cortex
VPA	Visual perceptual abnormalities
WM	White matter

Chapter 1

1.1 Introduction

Hallucinatory experiences, such as hearing voices when no one is present, or seeing objects that are not really there, are commonly thought of as symptoms of severe mental illness, most commonly 'schizophrenia'. However, research conducted during the past few decades has increasingly revealed evidence that these kinds of experiences are not confined to people who regard themselves, or are regarded by others, as mentally unwell. The surprisingly high prevalence of these experiences within the general population raises important questions about the nature of mental illness, and about whether common or different factors explain hallucinations in clinical and nonclinical groups. The work described in this thesis will make a small contribution to answering these questions by examining neural structure and functioning in healthy participants who vary in the extent to which they report hallucinations. As I prelude to this work, in this chapter I will review attempts to define hallucinations, evidence about their phenomenology (what they 'feel like' to the person experiencing them), their relationship with psychiatric diagnoses and their prevalence in both clinical and nonclinical groups.

1.2 Brief history of hallucination concept

The term hallucination is extracted from Latin hallucinere or allucinere, which means to wander in the brain (Choong, Hunter, & Woodruff, 2007). Experiences that would today be regarded as hallucinatory have been reported throughout recorded history; it has been argued that in ancient cultures, the occurrence of auditory verbal hallucinations (AVH) was often interpreted as a direct communication from the gods (Jaynes, 1976) . The first attempts to understand hallucinations within a modern scientific framework were made in the early 19th century. In 1845, the French psychiatrist Jean-Esquirol defined hallucinations as "conviction of perceiving a sense to which there is no external object" (Telles-Correia et al., 2015). For Esquirol, hallucinations were considered as a disorder in their own right. However,

by the end of the 19th century, researchers in the newly emergent discipline of psychiatry had begun to create diagnostic systems that attempted to identify discrete psychiatric disorders that corresponded to recognisable syndromes (clusters of symptoms), after which time hallucinations were typically regarded as a manifestation of a broader kind of psychiatric disorder (Bentall, 2004).

Today, the fifth edition of the American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013) defines a hallucination as "a sensory perception that has the convincing sense of truth of a true perception but that occurs without external stimulation of the specific sensory organ (Bentall, 2004). A definition that attempts to more precisely capture the phenomenology of these experiences was suggested by Slade and Bentall (1988), who defined a hallucination as 'any percept like experience that (a) occurs in the absence of an appropriate stimulus, (b) has the full force or impact of the corresponding actual perception, and (c) is not amenable to the direct voluntary control of the experience'.

Hallucinations are a common characteristic of mental disorders and may occur in any sensory modality. Auditory and visual hallucinations are considered to represent major signs of psychosis (Upthegrove et al., 2016); tactile, olfactory and gustatory hallucinations, in contrast, are thought to be uncommon in psychotic illness (Lewandowski et al., 2009). Auditory verbal hallucinations (AVH), also known as *hearing voices*, refer to the experience of verbal speech in the absence of anyone present.

Hallucinations may happen at sleep onset, in which case they are referred to as hypnagogic. Other types of hallucinations may occur during awakening and are referred to as hypnopompic (Ohayon, Priest, Caulet, & Guilleminault, 1996); however, these are phenomenologically distinct from the kind of hallucinations experienced by psychotic patients. A distinction has sometimes been made between true hallucinations and pseudohallucinations; true hallucinations are when the voice is perceived as coming from outside the body boundaries (external), whereas pseudohallucinations are defined as experiences where the voice is perceived as coming from inside the body (internal) (Looijestijn et al., 2013). The DSM (APA, 2015) notes that this distinction has never been shown to be important and today both types of experience would usually be considered to be hallucinations.

1.3 Phenomenology

In both research and clinical practice, the experience of hearing voices is currently the most discussed form of hallucination (Iudici et al., 2019). From a phenomenological point of view hallucinatory voices constitute a large and diverse community of phenomena characterised by multiplicity of manifestations, for instance, in terms of their clarity (through murmurs to voices), intensity (from whispers to shouts), linguistics (only sentences phrases, or full discussions), content (often demeaning, degrading or insulting) and mode of address (Henriksen et al., 2015). With regard to the latter, Kurt Schneider (1959) identified three forms that he regarded as 'first rank' symptoms of schizophrenia: audible thoughts, voices arguing, and voices heard commenting on one's own actions.

Hallucinations vary considerably in frequency. One study found that 12 % of psychiatric patients with AVH experience them 1-2 times a day; 36% recall hearing hallucinations for a small part of the day; 37% experience hearing hallucinations most of the day; and 15% report hearing hallucinatory voices all day (Nayani & David., 1996).

Patients often have difficulty in describing the features of their voices. For example, when are asked to talk about them some will say, for example, "Sometimes, I can't tell if I have a thought, whether it is a sound or if it's feeling I have" (Ratcliffe & Wilkinson., 2016). However, studies have also found that patients generally do not mistake hallucinatory voices from actual voices in the outside world (Zucker, 1928; Aggernaes, 1972).

Most of the voices reported by patients are negative in nature. For example, the voices may ask the patient to do something inappropriate (known as a command hallucination; Juninger & McGuire., 2001) or the voice may be offensive towards the patient. In some cases, AVH can appear to instigate manipulation, suicidal action, or even harm to others and society (Ratcliffe, 2017). However, positive voices – for example, voices praising the individual or offering reassurance and advice – are not uncommon and are experienced in about 50% of patients (Jenner et al., 2008).

Visual hallucination (VH) have been less studied than hearing voices. However, they may be coloured or black and white. Hallucinatory images are sometimes defined as dynamic and changing in size, shape and motion, but may also be fixed (Waters et al., 2014). Very often they co-occur with auditory hallucinations (Oorschot et al., 2012).

1.4 Relationships between hallucinations and mental illness

As noted at the outset, since the early 19th century hallucinations have commonly been considered evidence of psychiatric disorder. Psychiatric classification systems have continuously evolved over this period, culminating in the two systems that are most widely used today: the American Psychiatric Association's DSM-5 (APA, 2013) and the 11th edition of the World Health Organization's International Classification of Disease (WHO, 2018). Both are very similar and assume a categorical approach to classification (disorders are divided into discrete categories). It should be noted, before proceeding further, that this approach to classification has been increasingly disputed (Bentall, 2003). Recently, a number of alternative approaches have been proposed, including empirically developed taxonomies based on the statistical analysis of symptoms from a large number of patients (Kotov et al., 2017), network models that assume that symptoms do not have common underlying causes but occur in patterns because of the way that symptoms cause each other (Borsboom and Cramer., 2013) and transdiagnostic approaches such as the US National Institute for Mental Health's Reseach Domains Criteria programme (Insel et al., 2010) which dispenses with diagnoses altogether in favour of identifying common mechanisms for a range of psychiatric diagnoses.

Within conventional classification systems, hallucinations, especially AVH, are usually considered to be a symptom of schizophrenia. Auditory hallucinations are prevalent in schizophrenia patients between 50-70% (Poulet et al., 2005; Andreasen and Flaum., 1991; Slade & Bentall., 1988; Jardri et al., 2011). However, they are also reported by patients suffering from bipolar disorder or major depression: 11-63% of patients with bipolar disorder suffering from AVH (Toh et al., 2015; Baethge et al., 2005), and 15-19% of major depressed patients hallucinate (Gaudiano et al., 2009). Patients with diagnoses outside the psychotic spectrum may also report hearing voices, notably 46% of those diagnosed with borderline personality disorder, have been estimated to suffer from auditory verbal hallucination (Upthegrove et al., 2016). Hence, despite typically being attributed to schizophrenia, hallucinations are evident in a wide range of psychiatric conditions.

1.5 Relationship between hallucination and psychopathology

Despite the fact that hallucinations have typically been seen as evidence of mental illness by modern psychiatrists, increasing evidence has emerged in the past decades showing that a substantial minority of individuals experience voices and other kinds of hallucinatory experience without distress, and without seeking psychiatric treatment. This observation raises important questions about the dividing line between mental illness and healthy functioning. A better understanding of what distinguishes those where hallucinations leads to distress and those who experience hallucinations without negative effects may also inform future approaches to therapy.

Epidemiological studies show that hallucinations, especially AVH, are quite common in the healthy population. At the end of 19th century, the society for psychological research performed the first systematic study on hallucination of normal people in England. More than 14,000 men and women were interviewed by a team. Participants with apparent symptoms of physical or mental disorder were omitted. Almost 8% of men and 12% of women surveyed confirmed that there was at least one vivid hallucinatory experience. These hallucinations were often interpreted in a spiritual or paranormal context, and visual hallucinations were more often reported than auditory hallucinations. Half a century later, the society aimed, in a less detailed study, to replicate these finding and produced very comparable outcomes (West, 1948).

Current studies tend to indicate that people who not believe themselves to be mentally unwell, and do not feel that they need psychological therapy, often experience hallucinations. For instance, psychologists Thomas Posey and Mary Losch surveyed 375 university students. They found that 39% heard a voice talking spontaneously (an experience which Kurt Schneider claims is a first-class symptom of schizophrenia). Maybe more unexpectedly, 5% mentioned having discussions with their hallucinations.

Students are not representative of the entire population and some researchers have argued that while they report seemingly hallucinatory experiences, these experiences vary considerably from those described by mental health patients (Stanghellini et al., 2012). In 1991 American psychiatrist Allen Tien published the first research study using clinically appropriate hallucinations criteria on a epidemiological sample of 18,000 US adults (Epidemiological Catchment Area (ECA) Study). While the description of hallucinations used by Tien was derived from DSM-III-R, the results were almost identical to what the Society for Psychical Research had reported almost a century earlier. Tien, 1991 estimated that between

the 11 and 13 % of the ECA study participants experienced hallucinations at some point in life. Hallucination were reported twice as frequently by women, compared to men. Tien only acknowledged two differences between his results and the previous results from Britain: First l, the Society for Psychical Research study indicated that hallucinations were most often reported by those aged between 20 and 29 years, while the ECA found that hallucination are present throughout all ages but most frequently in old people. Second, the ECA study reported a lower frequency of visual hallucinations.

Epidemiological research in recent years has revealed similar findings. For example, Shevlin et al., (2007) using US National Comorbidity Study data found the following prevalence rates: 8.5 % for auditory hallucination, 7% visual hallucinations, and 7% tactile hallucinations. Hallucinations in one modality were reported by 11.4%, two types of hallucination by 3.9% and all three by 1.6% of the population (Shevlin et al., 2007). In an epidemiological survey of over 7000 people in the Netherlands, and after eliminating the experience of unexplained events due to substance use or physical illness, 1.7% of all participants reported clinically significant hallucinations, but an additional 6.2% had hallucinations which were considered not clinically significant because they were not connected to distress (Van Os et al., 2000). Poulton et al., (2000) reported a survey of 761 adults in Dunedin, New Zealand who had been tracked since childhood with very similar findings.

Similar findings have been reported outside the Anglo-Saxon world. A South Africa study estimated that 12.7% had experienced verbal or visual hallucination and an Australian study of young adults (13-17 years old) revealed that 8.4% had experienced either auditory or visual hallucinations (Temmingh et al., 2011; Scott et al., 2009).

Phenomenologically, hallucinations in nonclinical samples are similar to hallucinations in clinical samples. However, an important difference is that they tend to be predominantly positive in content (Jenner et al. 2008), with the consequence that the individual experiences them as benign and also feels less dominated by them (Honig et al., 1998)

1.6 Aetiology of psychotic symptoms

Considerable effort has been directed towards understanding the aetiology of psychotic disorders in general, and hallucinations in particular, and the plethora of theories on this topic cannot be adequately reviewed in the short space available here. However, it will be useful to consider briefly the relative role of genetic and environmental factors.

Until recently, it was widely assumed that psychotic conditions are primarily genetic in origin, mainly because family and twin studies consistently pointed to a heritability for these disorders exceeding 80 percent (Sullivan et al., 2003). On the rationale that such high levels of heritability precluded strong environmental influences, many researchers were skeptical that searching for such factors would be worthwhile (e.g Gottesman, 1991). This picture has been complicated by recent research using the methods of molecular genetics which have allowed the DNA of psychotic patients to be compared with samples from unaffected people (studies of this kind typically require very large sample sizes). Initially to the surprise of investigators, these studies failed to find any genes of major effect relating to psychosis; instead, a very large number of 'common variants' have been found, each conferring a very small risk of mental illness, together with a number of very rare variants (usually large deletions of DNA) which confer a high increased risk but which are thought to be responsible for very few cases of psychosis (Owen, 2012). A further complication is that recent reappraisals of the heritability concept have pointed out that even very high estimates of heritability do not preclude major environmental influences (Bentall, 2009).

From the late 1990s onwards, reports emerged that psychosis is associated with a very high rate of childhood traumas such as sexual abuse, emotional abuse, physical abuse and bullying. An early review of this evidence by Read et al., (2005) reported that the symptoms that are thought to be characteristic of psychosis, especially the hallucination, are at least as often linked to childhood abuse as many other mental illnesses. Summarising a large number of studies carried out until that date, they estimated a weighted average of 68.8% of female patients and 59.1% of male patients had experienced either sexual or physical abuse in childhood. This review led to a large number of studies, either assessing the relationship between childhood trauma and psychosis in epidemiological samples, comparing trauma histories between patients and controls or (in a small number of studies) prospectively following up children known to have experienced trauma to examine whether they developed psychosis in adulthood. These studies were meta-analysed by (Varese et al., 2012), who found a significant relation between childhood adversity and psychosis through is a synthesis of data

from 18 case-control studies, 10 prospective studies and 10 epidemiological samples. The risk of psychosis in people who had experienced childhood trauma was estimated to be approximately three times the rate in the healthy population, with evidence of a dose-response rate (so much higher odds ratios in those who had experienced the most severe abuse). The population-attributable risk (the number of patients with psychosis who would not be ill in the absence of childhood trauma) was estimated at 33%.

Given the abundance of evidence now suggesting that adverse childhood experiences play a causal role in psychosis, the importance of understanding the mechanistic pathways from trauma to symptoms has become evident. Surprisingly, very little empirical research has been carried out on this topic by neurobiologically-orientated investigators. However, Read et al., (2001, 2012) have proposed a traumagenic neurodevelopmental model which attempts to integrate what is known about the neurobiology of psychosis with insights from studies of trauma victims. This model, which the authors contrasted with a more conventional genetic vulnerability model, used evidence from children who were victims of trauma to argue that childhood trauma could lead to many of the biological changes observed in adult patients with psychosis, including increased sensitivity of the H-P-A axis, abnormal functioning of the domain system, and structural changes such as cortical atrophy and ventricular enlargement. Although widely cited, very few attempts have been made to test this model. However, in the only structural neuroimaging study to address the probable effect of trauma on adult brain structure, Sheffield and Heckers (2012) found reduced grey matter volume only in psychotic patients who had experienced abuse (structural scans from nonabused patients were normal).

The theoretical models so far considered have focused on psychosis in general, rather than specific symptoms. However, both epidemiological (e.g. Bentall et al. 2012; Sitko et al. 2014) and patient studies (e.g Wickham et al., 2014) have suggested that childhood trauma, especially sexual abuse, is an especially potent risk factor for hallucinations. This association has been found in nonclinical samples experiencing hallucinations as well as in patient samples (Andrews et al., 2008; Daalman et al., 2012). In patient samples, the content of hallucinations often follows themes related to their abusive experiences (Hardy, 2005).

Some efforts have been made to understand the cognitive and emotional mechanisms that might explain this specific association between hallucinations and childhood sexual abuse. One line of research has focused on dissociation, a state of emotional withdrawal from

the world which is thought to be a dysfunctional form of coping that is activated by unescapable trauma (Dalenberg et al., 2016). Typical dissociative experiences include derealisation, in which the world is experienced as unreal, and depersonalisation, in which the self is experienced as unreal. Dissociation is usually defined in phenomenological terms and there is little understanding of its neurobiological underpinnings, although it has recently been speculated that these might involve the autonomic nervous system (Porges, 2018; van der Kolk, 2015). It has been speculated that the altered conscious state of dissociation makes it harder for individuals to distinguish between internal mental contents and external stimuli (Longden et al., 2011). Consistent with this hypothesis, studies of clinical and also nonclinical samples have reported a robust association between scores on questionnaire measures of dissociation and hallucinatory experiences (Pilton et al., 2015).

1.7 Cognitive models of hallucinations

Cognitive models of hallucinations address the mental processes underlying these kinds of experiences and have mostly focused on AVH rather than hallucinations experienced in other modalities. In recent years, these models have been supplemented by findings from neuroimaging and neurophysiological research, which attempted to identify the neural substrates of the relevant cognitive mechanisms. In a recent review, Conde et al., (2016) identified four major models in the literature, although these overlap to some extent (in fact, two of the models are to a large extent identical).

Several models implicate abnormally vivid mental contents. For example, in a series of theoretical and empirical papers, Morrison and colleagues (Morrison, 2001; Morrison & Baker, 2000) argued that hallucinations are the consequences of the intrusion into the consciousness of uncontrollable thoughts and images, particularly based in past experience. This repetitive thinking and images are considered close to obsessive compulsive disorder patients' intrusive thoughts and images. Morrison argued that hallucinating people have abnormal meta-cognitive beliefs that these experiences are frightening as well as a sign of insanity. Hence, they attempt to inhibit the intrusions, but this makes them more persistent.

Waters et al. (2006) introduced a similar hypothesis, suggesting that AVH are auditory representations based on past memories (very much like Morrison's, (2001) intrusion idea).

Typically, if we recall something, the memory includes the context, when or where) it occurred. Water's et al. (2006) concluded that memories lack these contextual indications in patients with AVH. Waters et al., 2006 found evidence supporting this hypothesis in an experimental study. Patients had to remember form of words introduced on two distinct occasions; later, they had to recall not only what words had come together but also the occasion. More recently, Hardy colleagues (Hardy et al., 2020) pointed out that traumatic memories are often not contextual, which explains why AVH are often associated with previous trauma.

Aleman's et al. (2003) theory also focuses on mental contents, arguing that people with AVH have peculiarly vivid imagery. The confusion between externally and internally derived information in patients with hallucinations could, they argue, be the result of distortion in the balance between imagery and perception.

By comparison, other models focus on processes by which people determine if an experience (for example, a thought or inner speech) is created by themselves. Bentall (1990) indicated that AVH are the consequence of incorrectly attributing internal speech to an external source. In this context, inner speech, as defined by the Russian psychologist Lev Vygotsky, is the internalised use of words that facilitates thinking (Vygotsky, 1962). The process for differentiating internal thoughts from external stimuli is called source or reality monitoring. Bentall and Slade (1985), using a signals detection test, reported that patients with AVH had a tendency to believe that ambiguous signals (words hidden in white noise, were produced externally, which they argued was evidence for a source monitoring failure. This finding has been replicated many times (e.g. Brookwell et al., 2013). Many experiments have directly measured source monitoring for memories (e.g. Bentall et al., 1991). In these studies, participants listen to spoken words and also read their own words before later being presented with the words and being asked if they heard or read them. Patients with AVH commit more errors in these tasks and, in particular, mistake words spoken by themselves for words that have been presented to them. Again, this finding has been well-replicated (Brookwell et al.,2013).

As mentioned in section 1.6, a robust association has been found between hallucinatory experiences and dissociative mental states, suggesting that dissociation may be a mechanism that helps to explain hallucinations. In a study of patients with psychosis, Varese et al. (2012) measured childhood trauma, source monitoring, dissociative

experiences and hallucinations. Both source monitoring and dissociation predicted hallucinations but there was no association between the two mechanisms; dissociation but not source monitoring statistically mediated between trauma and hallucinations. This finding implies that impaired source monitoring and trauma-related dissociation may play separate and additive roles in the generation of hallucinatory experiences.

1.8 Findings from neuroscience

The development of neuroimaging research into AVH has been partly been derived by the models described above. These studies have enabled researchers to gain a preliminary understanding, especially in patients with schizophrenia, of brain regions and networks involved in these fascinating but potentially devastating symptoms. The studies can be divided into those that use structural and those that use functional analysis.

In patients diagnosed with schizophrenia AVH have been associated with changes in grey matter volume in brain (Modinos et al., 2013). Studies have reported that the volume of the insula is reduced along with reductions in the right temporal cortex, fusiform gyrus, left temporal gyrus, thalamus, and both cerebellum and cingulate cortex (Ford & Mathalon., 2005; O'Daly et al.,2007; Modinos et al., 2009). Reduction in cortical thickness is commonly reported in frontal, temporal and occipital cortices (Van Swam et al., 2012; Marti-Bonmati et al.,2007). Previous research has also identified correlations between grey matter volume loss and certain characteristics of the severity of hallucination: length of the hallucination, location, frequency and strength (Kubera et al., 2014). Analyses of white matter (WM) structures also indicated integrity deficiencies in connectivity between brain regions in patients with AVH (Seok et al., 2007).

Functional MRI (fMRI) experiments have been used to test psychological models of AVH that implicate misattribution or incorrect recognition of internal speech, for example by showing abnormalities in brain regions thought to be involved in voice recognition (Mechelli et al., 2007; Mou et al., 2013). Consistent with these models, functional MRI conducted when the brain is "at rest" in patient with AVH as contrasted with patients without AVH have indicated decreased activation in auditory cortex and language processing regions (Linden et al., 2011; Dierks et al., 1999; Diederen et al., 2013). Connectivity variation between areas

known to be involved in encoding and interpreting speech have also been observed in integrated magnetic resonance imaging (MRI) and positron emission tomography (PET) studies (Clos et al., 2014; Rish et al., 2013). In some hallucinatory state studies, in which patients were scanned while reporting when they heard voices, increased activity in the auditory system has been shown during speech processing itself (Linded et al., 2011; Looijestijin et al., 2013; Van De Ven et al., 2005; Sommer et al.,2008); it is possible that this kind of finding indicates a susceptibility to falsely recognising words in naturally occurring or aberrant sounds from the environment. The secondary auditory cortex is associated with perception of sounds, and decides the source of a sound; hence resting activation in this region may also contribute to erroneous perception of words in nonverbal external noise (Northoff & Qin., 2011; Sugimori et al., 2014).

It has been argued that auditory and speech processing problems are the consequence of an executive frontal functional impairment, which is a basic neuronal dysfunction and essential characteristic of schizophrenia (Freedman & Brown., 2011). These difficulties would affect not only the processes underlying AVH but also other perceptual disturbances such as thought insertion (Aleman et al., 2003; Hoffman et al., 1999). Some authors have argued that alterations in the balance between top-down modulation and bottom-up processing is key to AVH in schizophrenia (Allen et al., 2012). On this view, the top-down processes involve the direction of attention to essential subjects and signs and are disordered in patients with AVH, leading to the false detection of external stimuli. Bottom-up complexity is due to decreased rest or spontaneous activity in the auditory cortex, which leads to more 'noise' and more confusion in the higher brain regions (Allen et al., 2012; Amad et al., 2014). Whereas some reports point to abnormalities in frontal language areas (Diederen et al., 2012) others highlight the role of the auditory cortex, which is thought to be both 'turned on', displaying increased function in its intrinsic state, and 'turned in' to detecting verbal stimuli, leading to attention being focused on internal stimulation rather than external stimuli (Northoff & Qin., 2011; Hugdahl., 2009; Ford et al., 2009).

There is evidence that endorses either an auditory model or other models, what can most bother patients is the inability to disregard voices as they arise and to concentrate on other items happen in their surroundings. The lack of ability to suppress and inhibit voice is a significant aspect of clinical AVH, remarkably few studies have specifically examined the relationship between executive function in general and suppression in particular and AVH.

The cognitive function in AVH have been examined by Water et al., 2006, in relation to what these authors call impairment of intentional cognitive inhibition, which is the failure to voluntarily control and prevent intrusive thinking. Failure to observe cognitive inhibition may have neuronal positioning in the frontal lobes and subsequent prefrontal inhibitory abnormality in AVH patients (Hugdahl, 2015b). (Aleman & Vercammen, 2013; Allen et al., 2008) reported that the prefrontal cortex critically involved in cognitive control and executive function in AVH patients.

Functional cerebral asymmetry studies have also attempted to integrate functional brain imaging findings with structural evidence. Auditory-related activation asymmetry, for example, was found to be attenuated in schizophrenic patients relative to controls. This further supports claims that are based on structural alteration data linking the symptoms of AVH in schizophrenia to dysfunction in left-hemispheric, particularly auditory and language-related areas (Zhang et al., 2008; Kim et al., 2012). Kühn & Galliant (2012) investigated whether neuroimaging abnormalities were related to trait or state aspects of hallucination; they found that the experience of AHVs was associated with increased activity in areas related to speech production, primarily Broca's area, while trait susceptibility to AVH appeared to be linked more to abnormalities in areas linked to processing auditory stimuli, especially superior temporal and auditory cortical areas. Magnetic resonance spectroscopy studies showed some findings for the association between the severity of AVH and left Heschl gyrus metabolism as far as brain metabolism is concerned (Homan et al., 2014; Nenadic et al., 2014).

Currently, only minimal diffusion tensor imaging (DTI) work has extended this work to study the connection between white matter structural changes and auditory verbal hallucinations (Ćurčić-Blake et al., 2015; de Weijer et al., 2011). Evaluation of water spatial diffusion (anisotropy) is useful in characterising the microstructure of white matter and may provide further evidence that AVH are due to pathological brain changes (Pasternak et al., 2018). The integrity of the axonal and myelin membranes has been shown to affect fractional anisotropy (FA), the direction of water diffusion in the brain (Beaulieu, 2002). The findings of these studies have been contradictory. Some showed higher FA in patients with AVH, which implies increased connectivity within the memory and language networks (de Weijer et al., 2013; Hubl et al., 2004; Mulert et al., 2012). Others have shown an FA decline in the same structures (Benetti et al.,2015; Catani et al.,2011; Wigand et al., 2015; Oestreich et al.,2016). These inconsistencies may be attributed to the clinical characteristics of the sample

employed, for example the varying duration of their illness and the drugs they have been prescribed. For chronic patients with recurrent condition, for example, different results might be obtained compared to patients in the early phase of a first episode of psychosis. Furthermore, a reduction in FA may not necessarily mean aberrant integrity, instead may reflect variation in factors such as axonal dimensions or the existence of fibre crossings (Hoeft et al., 2007; Soares et al., 2013).

The arcuate fasciculus (AF) is a large fibre bundle that connects Wernicke's area, the spoken perception area at the posterior end of the superior temporal gyrus, to Broca's speech production area in the left inferior frontal gyrus, with a corresponding extension on the right side (Alderson-Day et al., 2015; Hubl et al., 2007). The AF consists of short fibres that connect different locations within regions and long fibres connecting between regions (Catani et al., 2011; Catani & Thiebaut de Schotten., 2008). In healthy people, the left AF volume is slightly greater than the homologous right volume, with stronger asymmetry between hemispheres in AVH patients (Fernández-Miranda et al., 2015; Ocklenburg et al., 2013). Reduced fractional anisotropy values have been reported in the left AF in patients with AVH, reflecting abnormalities in white matter organisation along the AF extension (Geoffroy et al., 2014). Studies also indicated an increase in the volume of white matter in some arcuate fasciculus regions (Mitelman et al., 2007).

1.9 Summary

In this chapter I have reviewed the available evidence on the nature of auditory-verbal hallucinations, the psychological processes that might be involved in their occurrence and the neurostructural and functional abnormalities that may underlie these processes. In this account, I have mainly focused on studies of clinical participants (usually diagnosed with schizophrenia) but the epidemiological data reviewed indicates that many people experience AVH without being considered to be mentally ill. One explanation for this phenomenon is that psychotic experiences such as hallucinations lie on a continuum with healthy functioning, an idea which will be examined in detail in the next chapter (chapter 3).

Chapter 2

MRI

2.1 Introduction

Raymond Damadian first discovered that abnormal tissue had different NMR (nuclear magnetic resonance) parameters than healthy tissue at the end of the 1960s, opening the possibility that NMR could be used for the purposes of tissue characterisation (Blink, 2004). In 1974, the first NMR image of a rat tumour was reported, building on his discovery. The first powerful superconducting scanner was built by Damadian and his team in 1977. After that, Paul Lauterbur took the lead in the same field and developed MRI imaging as it is known today. At that point, the names of the approach was changed from Nuclear Magnetic resonance (NMR) to Magnetic Resonance Imaging (MRI) in the hope that it would be more widely accepted in the medical community (Blink, 2004). In the 1980s, medical imaging equipment manufactures started to produce commercial scanners. After that, further improvements in the software and hardware made the imaging faster and easier to do. These developments were accompanied by new applications such as T1, fMRI, perfusion and DTI.

2.2 The Phenomenon of Spin and Nuclear Magnetic Resonance

To create an image in MRI, signals are detected from the nuclei of hydrogen atoms. The nucleus of the hydrogen atom includes a single proton and a single electron. The electron is negatively charged, while the proton is a positively charged. The proton rotates around itself (spinning), leading to two properties: first, angular momentum (associated with the rotating mass) and, second magnetic momentum, which causes the proton to act as a small magnet. External magnetic fields can affect the proton (Weishaupt et al., 2008). Whence, when the proton of the hydrogen atom put in the external magnetic field, it will align its spin or magnetic moment with the direction of the magnetic, like a compass needle, a process known as precession. The precession or Larmor frequency is the magnetic field which affects proton spin, expressed by the equation $\omega 0 = \gamma 0 . B0$, where:

ω0 is the Larmor frequency in megahertz (MHz).

γ0 is the gyromagnetic ratio.

B0 is the strength of magnetic field in Tesla (Weishaupt et al., 2008).

2.3 T 1 structural Imaging (Volumetric Measurements)

3D isotropic acquisition enables high resolution multiplanar representation of structure without extra scans from various directions, as shown in Figure 2.1. 3D T1 weighted images therefore have great value for disease assessment (Bottomley et al., 1987) and for assessing the effects of aging on the brain (Lee et al., 2018). The T1 3D images, when processed using modern imaging analysis software, can also be used to generate information about cortical thickness and volume. For example, the imaging analysis tool FreeSurfer uses affine transformation to integrate information on voxel intensity related to the probability distribution of tissue groups with data on the spatial relationships of voxels with adjacent structures registered on manually labelled atlases. The atlas used in the analysis enables the measurement of average cortical thickness and volume in different areas in the brain (Desikan et al., 2006). Changes in cortical thickness and subcortical volumes have been widely documented in patients suffering from neurological disorders (Fujita et al., 2019). The grey matter thickness and volume extracted from 3D T1 allows researcher interested in hallucinations to explore differences between patients and healthy groups in terms of increases or reductions of brain volume in specific areas. This method allows researchers to correlate data extracted from the image with data from questionnaires completed by the participants.

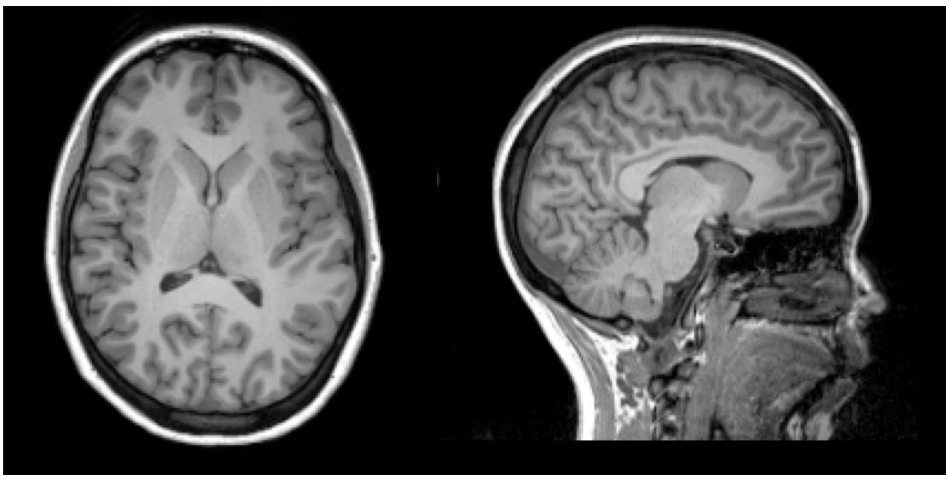

Figure 2.1: 3D T1 provide information about cortical and subcortical change in volume and thickness.

2.4 fMRI (functional magnetic resonance imaging)

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive technique used to study brain activation. fMRI measures changes in blood oxygenation and blood flow related to neuronal activity. When researchers study human brain function in vivo, the flow of oxygenated blood changes in response to a specific task or when the brain is at rest. fMRI thereby provideds unprecedented access to the inner working of the human brain for researchers, allowing them to study how the brain processes information.

The BOLD contrast is that the most common technique used in fMRI. Two physical phenomena called diamagnetism and paramagnetism are closely linked to the BOLD (blood oxygenated haemoglobin dependent) contrast (Filippi, 2009). In order to understand the effect of BOLD, it is necessary to understand that, when a diamagnetic substance is subjected to an external magnetic field, this field decreases slightly, while paramagnetic substances tend to increase it. Hence, a spatial distortion of the magnetic field occurs near the interface of paramagnetic and diamagnetic substances. Most human tissue is generally diamagnetic, whereas oxygenated deoxyhaemoglobin is paramagnetic. Neuronal activation leads to a wash-out of deoxyhaemoglobin and increased concentration of oxyhaemoglobin locally. Compared to deoxyhaemoglobin, oxyhaemoglobin is diamagnetic and has the same magnetic properties of ordinary tissue, causing a more homogenous magnetic field and improved signal intensity in T2* weighted images.

In summary, the basic concept of BOLD is that the haemodynamic response to brain activation leads to a decrease in deoxyhaemoglobin which, in turn, leads to increased field homogeneity and therefore, a series of T2* weighted images with higher signal intensity. Hence, by measuring this signal enhancement it is possible to detect neuronal activation (Filippi, 2009). This effect depends on the following factors: cerebral blood flow (CBF), cerebral blood volume (CBV), and the metabolic rate of oxygen consumption (CMRO2). CBF goes up after a stimulus as more oxygen is delivered to the site of neuronal activation.

fMRI has been widely used to research the neurobiological basis of severe mental illness and range of different of paradigms have been implemented for this purpose (Mulert & Shenton, 2014). Functional MRI methods are therefore useful tools for probing abnormal neural processing in particular brain regions. For example, fMRI has been used the demonstrate detectable differences in neural activation between patients with schizophrenia and healthy controls (Kim et al., 2009). Specifically, fMRI studies have shown dysfunctional brain activation in the prefrontal and temporal cortices of affected patients (Madre et al., 2013). As described in later chapters, the technique has been used to investigate abnormal auditory and language processing in patients who hear hallucinatory voices.

2.5 DTI (diffusion tensor imaging)

MR images can be triggered by applying a magnetic field gradient, causing the motion (diffusion) of water molecules in the direction of the field gradient. In WM (white matter) fiber tracts, the diffusion is anisotropic (directionally dependent); the motion of water molecules in directions not parallel to their orientation is impeded by barriers such as axonal membranes and myelin sheaths whereas, in the direction of fiber tract orientation, diffusion is maximum. The diffusion tensor is a three-dimensional spacial mathematic model of diffusion, which has specific properties that allow complex physical phenomena to be quantified. From diffusion measurements in several different tissue matrices, data can be derived and used to create the tensor in order to estimate the diffusivity in any arbitrary direction (Jellison et al., 2004). From diffusivity measurements in at least six noncollinear directions, it is possible to derive the tensor model in the form of a 3X3 matrix. With six

degrees of freedom, the tensor matrix is diagonally symmetric (Dij = Dji). hence a minimum of six encoded measurement required to accurately describe the tensor. However, the accuracy of the tensor measurement will improve when using more than six encoding directions for any arbitrary orientation.

Diagonalisation is the process by which the tensor matrix is subjected to a linear algebraic procedure, generating major, medium and minor ellipsoid sets of eigenvectors along the principal axes. It is fitted to the data and the corresponding three eigenvalues (λ_1 λ_2 λ_3), represent the apparent diffusivities through these axes as shown in the Figure 2.2 below (Jellison et al., 2004). These eigenvalues provide information about microstructural composition of the relevant fibre tract. The total of the eigenvalues provides the fractional anisotropy (FA) value. The eigenvalue λ_1 indicates the axial diffusivity (AD) value and the mean of the three eigenvalues ($\lambda_1 + \lambda_2 + \lambda_3$) provides mean the diffusivity (MD) value. The mean value for two of the eigenvalues ($\lambda_2 + \lambda_3$) provides the radial diffusivity (RD) value. hence, calculating the eigenvalues across the three main axes of diffusion creates an opportunity to determine microstructure alterations in white matter (WM) (Mulert & Shenton, 2014).

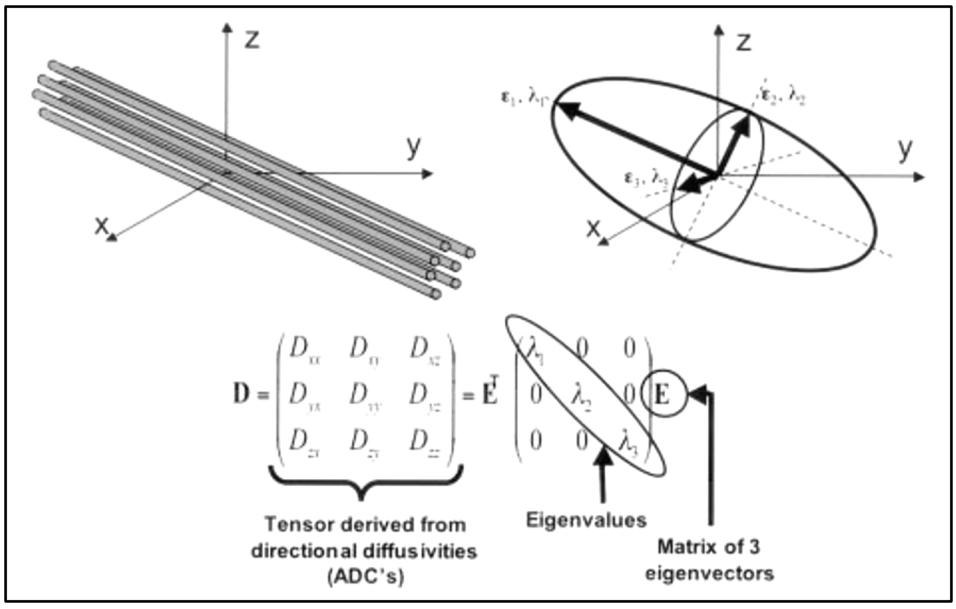

Figure 2.2: In respect to scanner geometry (x, y, z axes), the fibre tract in the top left has an arbitrary orientation and directional dependence (anisotropy) on diffusion measurements. Top right is the ellipsoid orientation characterised by the three eigenvectors (λ1 λ2 λ3). The bottom is the ellipsoid model fitted to set of at least six noncollinear diffusion measurements. The three

tensor eigenvalues mathematically translate to the degree that the tensor differ from one another. The fractional anisotropy (FA) is one of the most commonly used among several anisotropy metrics (Jellison et al., 2004).

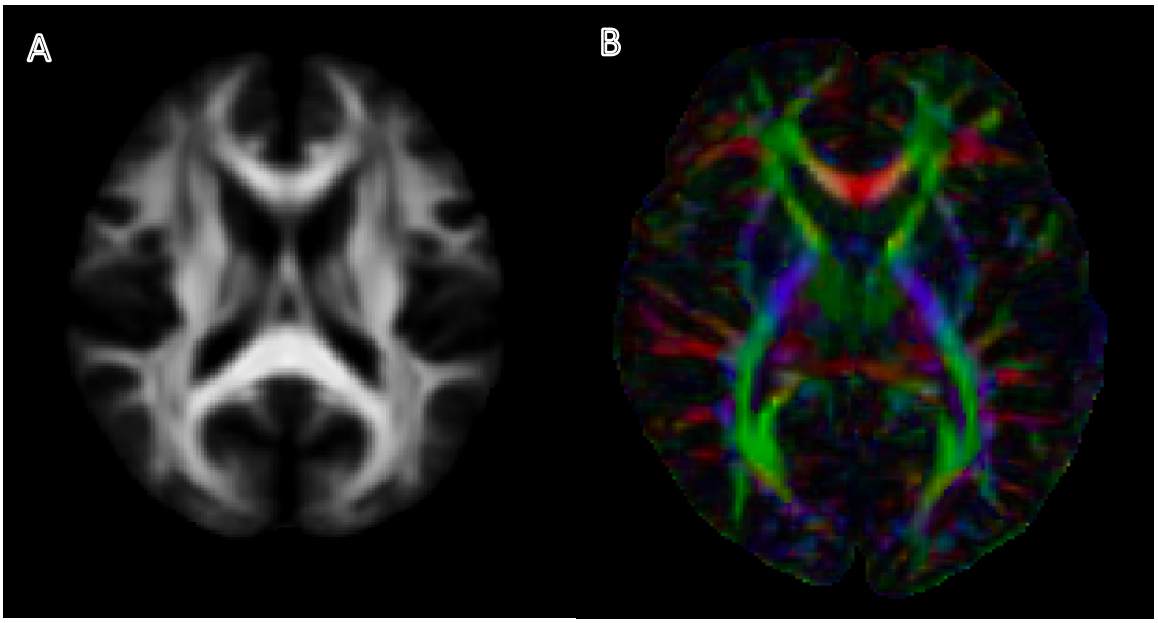

Figure 2.3: (A) without directional information, is FA map. (B) combined FA and directional map coloured.

In the Figure 2.3 above, in image (A) there is not any information about the direction of the diffusion. In image (B) the direction of the diffusion is obvious. The red colour shows the diffusion direction from the left to the right. The green colour shows the diffusion from the anterior to the posterior direction. The blue colour shows the diffusion from the superior to the posterior direction. DTI therefore provided measurements of WM integrity, for example between frontal and temporal lobes (Kubicki et al., 2007). Moreover, DTI provides information how the components of this network are related and how these regions communicate (Allen et al., 2012). In addition, DTI provides information about the white matter size and, by measuring the water concentration caused by axons or glia cells integrity, whether this size is currently increasing or decreasing. (De Weijer et al., 2011).

2.6 Neuroimaging Studies

Neuroimaging studies to date support the existence of systemic and functional changes in the brains of individuals who experience hallucinations. 3D T1 provides information about associations between alterations in the thickness and volume of grey matter in specific brain regions and hallucination proneness. Previous studies have found abnormalities in the auditory cortex and language. Complementary to this, fMRI provides information about brain activation during the execution of active tasks and about metabolic and functional abnormalities in the speech and language areas. Finally, DTI provides information about the microstructure of white matter and the integrity between brain regions. Together, the findings from these different imaging techniques can be used to understand the neural changing in brain areas related to the auditory and visual hallucination.

Chapter 3

The Continuum Hypothesis of Hallucinations: Evaluating the Launay-Slade Hallucination Scale as an Instrument to Capture Visual and Auditory Hallucination Proneness in Neuroimaging Studies

3.1 Introduction

Hallucinations are perceptual experience that occur in the absence of the appropriate stimuli (Slade & Bentall, 1988) and are often experienced as overwhelming by the individual (Powers, Kelley, & Corlett, 2017). They have been regarded as a cardinal symptom of schizophrenia and are found in 60%-70% of total patients (Jardri et al., 2011). Within the spectrum of schizophrenia symptoms, hallucinations were described by Crow (1980) as belonging to a 'positive syndrome' of experiences and behaviours that would normally be absent; this syndrome also included various kinds of delusions (irrational beliefs, of which the most common kind is paranoid or persecutory delusions). Crow contrasted the positive syndrome with the 'negative syndrome', which he thought consisted of deficits in experience and behaviour such as flat affect and emotional withdrawal. Since Crow's model was originally proposed, it has been expanded and numerous factor-analytic studies have shown that the positive syndrome can be reliably distinguished from syndromes of negative symptoms, cognitive disorganisation, depression and mania (van Os and Kapur, 2009).

In this chapter, I briefly review evidence that psychotic experiences in general, and hallucinatory experiences in particular, exist on a continuum with normal functioning. I then introduce the Launay-Slade scale, a measure of hallucinations used in my neuroimaging studies, and evaluate its psychometric properties and suitability for this purpose.

3.2 The continuum hypothesis

In the previous chapter, I briefly reviewed evidence showing that hallucinations are not only experienced by patients diagnosed as suffering from psychotic disorders but also in a

substantial minority of the general population (Alderson-Day et al., 2019; Fonseca-Pedrero et al., 2010; Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Johns, Nazroo, Bebbington, & Kuipers, 2002; Ohayon, 2000). This observation raises the question of the extent to which nonclinical hallucinations are similar or dissimilar to those experienced by patients.

A very large psychological literature, beginning with the work of Paul Meehl (1962), has explored the idea that psychotic experiences exist on a continuum with health functioning. Meehl rejected the idea of a simple continuum, instead arguing that there is a large (he estimated about 10% of the population) taxon (group of people) who inherit a cognitive vulnerability to schizophrenia which he termed 'schizotaxia'. He proposed that, of the people in this taxon, only a proportion who were exposed to severe stress would develop psychosis, but the rest would show 'schizotypal' personality characteristics. A similar idea was developed by Gordon Claridge (1985), who argued for a continuum of 'schizotypy' but that additional stressors were required for highly schizotypal people to develop mental illness. These proposals were supported by empirical studies using simple questionnaires which showed that a surprising number of ordinary people (in most studies, university students), when asked, reported quasi-psychotic hallucination-type experiences and odd beliefs. A persistent debate within this literature has been whether schizotypy is fully dimensional or whether, as originally proposed by Meehl, there is a latent schizotypal taxon. Attempts to address this problem have entailed the development of new statistical methods, known as taxometrics, which have sometimes been reported as revealing a schizotypal taxon (Lenzenweger, 2010) and sometimes supported a continuum (Rawlings et al. 2008).

A complication is that many of these studies have treated schizotypal traits as existing on a single continuum whereas, as we have seen, psychotic symptoms fall into five syndromes (if depressive and manic symptoms are included). In fact, beginning with an early study by Claridge (Bentall, Cladidge & Slade, 1989; Mason, Claridge & Jackson, 1995; Claridge et al. 1996; Mason & Claridge, 2006)) have consistently found that schizotypal traits fall into three dimensions conforming to the positive, negative and disorganized syndromes of psychosis (studies have typically not included depressive and manic experiences). Hence, in considering whether psychotic experiences and schizotypal traits exist on a continuum, it may be important to focus on specific types of psychotic experiences.

Baumeister, Sedgwick, Howes and Peters (2017) have recently reported a systematic review of the relevant evidence with respect to hallucinations, contrasting three models: a

diagnostic discontinuous model (in which hallucinations in healthy participants are considered to be part of normal human variation and distinct from clinical hallucinations), a quasi-dimensional model (in which healthy hallucinations are considered to be midway along a spectrum with clinical hallucinations but in which only those with frequent and distressing hallucinations have a need for care) and a fully dimensional model (in which clinical and nonclinical hallucinations are indistinguishable and need for care is determined by other factors) (see Figure 3.1). They focused particularly on auditory-verbal hallucinations and considered a wide variety of evidence including the phenomenology of the experiences, individual's beliefs about their experiences and the relationship between hallucinatory experiences and more broadly defined psychiatric disorder. Many similarities were noted between nonclinical and clinical hallucinations although the latter occurred more frequently and were more often negative in content. Both types of hallucinations were associated with childhood trauma. Overall, Baumeister et al. (2017) rejected the dimensional model, but found that the evidence did not clearly adjudicate between the quasi-dimensional and fully dimensional models.

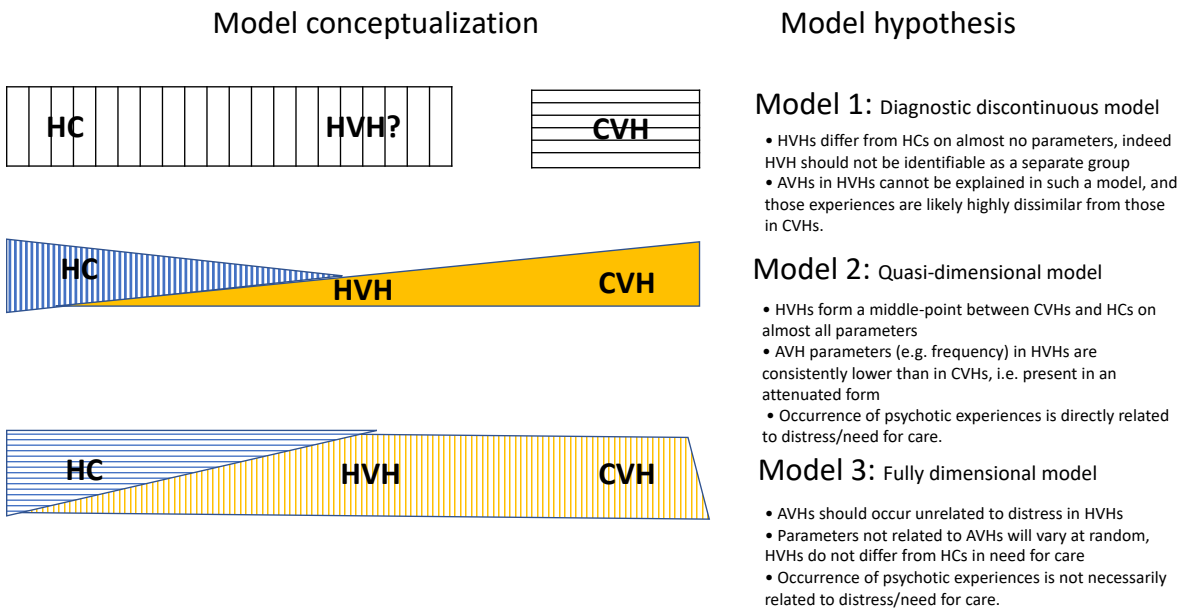

Figure 3.1: Schematic diagram of the three models reproduced from Baumeister et al. (2017).

3.3 The Launay-Slade Hallucination Scale

Within the schizotypy literature, the term 'predisposition to hallucinations' has been used to describe the tendency to report subclinical hallucinatory-like experiences. One of the most

widely used scales designed to measure this predisposition is The Launay-Slade Hallucination Scale (LSHS), which has 12 items, and which was first published in 1981 (Launay & Slade, 1981). A search of Google Scholar using the search term "Launay-Slade Hallucination Scale" retrieved no less than 1,010 articles (search date: 23rd October 2020).

Items cover frank hallucinatory experiences (e.g. "I have been troubled by hearing voices in my head"; "On occasion I have seen a person's face in front of me when no one was in fact there"), vivid imagery experiences (e.g. "The sounds in my daydreaems are usually clear and distinct"; "The people in my daydreams seem to true to life that I sometimes think they are") and intrusive cognitions (e.g. "No matter how hard I try to concentrate, unrelated thoughts always creep into my mind"; "Sometimes a passing thought will seem so real that it frightens me"). The authors of the scale reported that the items conformed to the Rasch model, which is to say that the formed a graded ladder of difficulty (probability of endorsement). The scale was slightly modified in 1985 and called the Launay-Slade Hallucination Scale–Revised (LSHS-R), and was shown to have a high level of test-retest reliability (Bentall & Slade, 1985), and subsequent research has confirmed that scores are highly stable over time (Aleman et al. 1999).

The scale was further modified in 2000 by the addition of four items measuring specifically visual experiences (Morrison et al., 2000). These authors considered that their version of the scale might be multi-factorial and, with these additional items, claimed to extract two factors corresponding to visual and auditory experiences. However, the two factors accounted for only 38% of the variance, the reliability of the verbal factor was marginal (0.64) and some items loaded significantly on both factors (e.g. 'I hear a voice speaking my thoughts aloud' had a factor loading of .54 on the verbal factor but also a loading of .33 on the visual factor). Other authors have also reported a multi-factorial structure, but the factor structures have differed according to the analytical approaches taken (for example, Aleman et al. 2001, found that the scale yielded three factors which they interpreted as tendency towards hallucinatory experiences, subjective externality of thought, and vivid daydreams) and the samples assessed (for example, Levitan et al. 1996 administered the scale to a large group of psychiatric patients and extracted four factors corresponding to vivid thoughts, perceptual aberrations, vivid daydreams and psychotic hallucinations).

Other scales have been developed to measure hallucinations. For example, in a series of studies Barrett et al. (1992, 1993, 1994) used a nine-item questionnaire constructed to

capture both quantitative and qualitative information to investigate hallucinatory experiences in student samples. A more detailed measure is provided by the Cardiff Anomalous Perception Scale (Bell et al. 2006), which is designed to be suitable with clinical samples, which includes 32 items tapping a wide range of anomalous experiences, each with three sub-questions. It is perhaps because of the complexity of this scale that it has been used much less extensively than the Launay-Slade Scale (the search term "Cardiff Anomalous Perceptions Scale" yielded just 90 articles and the source papers for the two scales have been cited 239 times vs 588 times in Google Scholar as of October 23rd 2020).

Despite the apparent simplicity of the Launay-Slade Scale, many studies have used it to replicate in healthy participants findings that have been reported in psychiatric patients. For example, high scorers on the scale, like psychiatric patients with hallucinations, have been found to show impaired source monitoring (e.g. Bentall and Slade, 1985), high levels of suggestibility (e.g. Young et al. 1987), high levels of dissociation (e.g. Varese et al. 2011) and high levels of childhood trauma (e.g. Berry et al. 2018) (see Chapter 1 for evidence that these factors play a role in hallucinations in clinical samples).

The scale has also been used to investigate the neural correlates of hallucinatory experiences in neuroimaging studies. For example, Barkus et al. (2007) found that healthy participants scoring highly on the scale showed impaired source monitoring (as previously reported by Bentall and Slade, 1985) and that, in these participants, false alarms on the source monitoring task were associated with activation in the superior and middle temporal cortex. More recently, Spray et al. (2018) assessed healthy individuals' hallucination proneness by the Launay Slade Hallucination Scale (LSHS) before her participants underwent imaging study (volumetric and white matter microstructure) investigations. A negative correlation was reported between the hallucination severity scores (LSHS) and left superior temporal gyrus volume. In addition, a negative correlation was detected between LSHS scores and white matter fractional anisotropy (FA) in the bilateral superior temporal gyrus. Finally, a negative correlation was observed between LSHS scores and orientation dispersion index (ODI) in the left superior temporal gyrus. These findings were interpreted as indicating that hallucination proneness is associated with reduced functional integration in the superior temporal gyrus, possibly due to reduced dendritic complexity in that region.

Purpose of this study

The Launay-Slade Hallucination Scale would appear to be ideally suited for the research to be reported in this thesis, in terms of its brevity, acceptability to healthy samples, its validity as attested by its known correlates with psychosis related variables, and its previous track record in imaging studies. However, research findings on its factor structure have been inconsistent, possibly partly because of the different kinds of samples employed in different studies. Were it possible to pick out clearly distinct verbal and visual factors, as claimed by Morrison at al. (2000), this would have implications for the utility of the scale in imaging analysis.

In the rest of this chapter, I will report preliminary analyses of the Launay-Slade data collected from the participants who took part in the imaging studies reported later. The purpose of these analyses was to demonstrate the convergent validity of the scale against other measures and also to check the LSHS's psychometric properties, to test establish whether the factor structure reported by Morrison et al. (2000) could be replicated and, if necessary, select items suitable for the imaging analyses reported in later chapters of this thesis.

The convergent validity of the scale was tested by establishing its correlations with other measures. As noted above and in Chapter 1, hallucinations form part of the positive psychosis/schizotypy spectrum along with delusional beliefs. For this reason, it was expected that LSHS scores would correlate with delusional beliefs and, for this reason, we included a widely used measure of paranoid thinking. As noted in Chapter 1, there is also consistent evidence that hallucinations are associated with dissociative experiences and, for this reason, we also included a dissociation measure.

3.4 Methodology

3.4.1 Participants

An online survey version of the modified $LSHS_{(M)}$ scale employed in this study was created using Qualtrics software. A link to the Qualtrics survey was distributed by email to students and staff at the University of Liverpool. Seventy-five participants completed the $LSHS_{(M)}$ questionnaire online. Seventy-five participants agreed to visit the laboratory to be briefed

and consented for the MRI studies, at which point they were asked to complete the paranoia and dissociation measures together with other measures not reported here. This final sample consisted of 23 male and 52 females with an average age of 25 (SD=7.94; range, 19-66), of whom 69 eventually undertook the MRI protocol. All participants who visited the laboratory were compensated £10 for their time.

3.4.2 Measures

3.4.2.1 The Modified Launay-Sade Hallucination Scale

This version of the LSHS included 16 items as originally developed by Morrison et al., (2000). The scale (see Appendix A1) consists of general ("sometimes my thought seems as real as actual events in my life"), auditory ("I have been troubled by hearing voices in my head") and visual ("I see shadows and shapes when there is nothing there") items. The participants were required to report the degree to which each statement described their previous experiences (0 = certainly does not apply, 4 = certainly applies).

3.4.2.2 The revised Persecution and Deservedness scale (PaDS)

The PaDS-r. was modified and easier to complete version of an earlier version of the same scale (Melo, Corcoran, Shryane, & Bentall, 2009), which was developed to measure both the severity of paranoid ideation and also whether or not any perceived persecution was believed to be deserved. The original version of the scale, which has been shown to be suitable for use in both clinical and nonclinical samples (Elahi et al. 2017), included 10-items, each with two parts, the first measuring persecutory ideation and the second measuring deservedness, reflecting a theory by Chadwick and Trower (1997) that paranoia can be divided into two types according to whether persecution is believed to be deserved; however, paranoia with low deservedness is very rare in nonclinical samples (Bentall & Udachina, 2013). The revised version was designed to be simpler to administer and score and consists of 10 items (see Appendix A2), eight of which measured persecutory experiences ("My friends often tell me to relax and stop worrying about being deceived or harmed") and two items which measure the extent to which persecution is believed to be deserved ("People will almost certainly lie to me"); the latter items are not included in the present study. Participants responded on a five-point

Likert scale (0 = strongly disagree, 4 = strongly agree). The total paranoia score was calculated by summing the relevant items (0 – 32).

3.4.2.3 The Dissociation Experiences Scale (DES; Bernstein & Putnam, 1986)

The DES is a widely used measure of dissociative states (see Appendix A3). The scale consists of 28 items. The participants were required to report the degree to which each statement describes their previous experience by moving a cursor across a 100-mm line at the appropriate place, with anchors "never" and "always". Before examining the correlation between the DES and the $LSHS_{(M)}$, item 27 was removed (because it explicitly refers to hallucinations).

3.5 Data Analysis

Statistical analysis was performed using SPSS 25. Exploratory factor analysis was conducted using principal components analysis extraction and oblimin rotation (to allow subscales to correlate). The method of the analysis replicated that used in a previous study (Morrison et al., 2000) with the exception that the Kaiser criterion (eigenvalue > 1) was used to extract factors in the first instance, after which, following the previous researchers, two factors were extracted. Correlations were then performed between $LSHS_{(M)}$ (total and subscale scores) and PaDS and DES.

3.6 Results

Reliability and Factor Structure of Modified $LSHS_{(M)}$

The distribution of the $LSHS_{(M)}$ was near-normal, see Figure 3.2, as reported in a previous study (R. P. Bentall & Slade, 1985). Cronbach's alpha coefficient was used to measure

reliability and, for the entire scale = .85; previous studies have recommended that an alpha of .70 or above indicates acceptable reliability (Lance, Butts, & Michels, 2006).

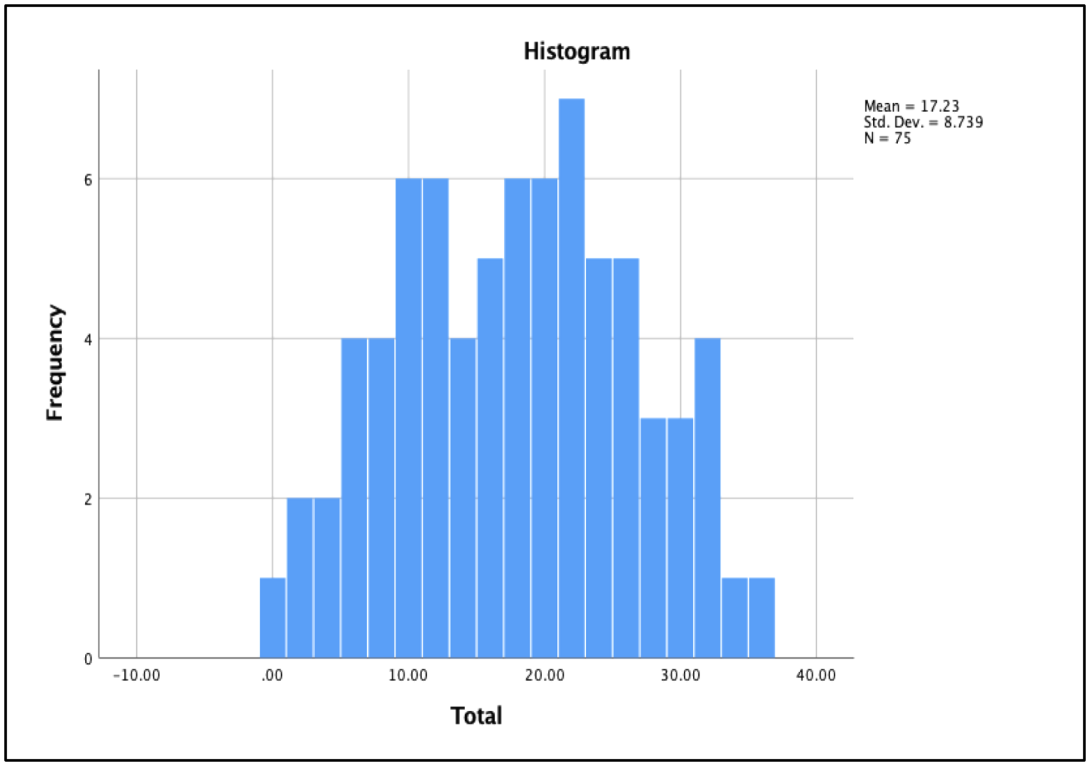

Figure 3.2: Show the $LSHS_{(M)}$ scores distribution.

When a Kaiser criterion was used, four factors were extracted with eigenvalues of 5.051, 2.051, 1.624 and 1.345, accounting for 62.94 percent of the variance in scores but the factors were uninterpretable. The factor analysis was then repeated, excluding item 11 (because of low endorsement rate) and extracting two factors as recommended by Morrison et al. The resultant factor values are shown in Table 3.1 and the structure matrix for this analysis is shown in Table 3.2, which also shows Morrison et al. (2000) factor scores. Note that the total variance accounted for (45.96%) shown in Table 2.1 is higher than the 38% reported by Morrison et al.

Table 3.1: Eigenvalues and total variance explained with two factors extracted.

Component	Eigenvalue	% of variance	Cumulative %	Extraction sums of squared loading			Rotation sums of squared loading
				Total	% of variance	Cumulative %	Total

1	5.011	33.408	33.408	5.011	33.408	33.408	4.349
2	1.883	12.556	45.963	1.883	12.556	45.963	3.622
3	1.624	10.827	56.790				
4	1.145	7.633	64.423				
5	.954	6.362	70.785				
6	.896	5.975	76.759				
7	.604	4.030	80.789				
8	.543	3.618	84.407				
9	.517	3.446	87.853				
10	.481	3.210	91.062				
11	.349	2.329	93.392				
12	.313	2.090	95.482				
13	.254	1.696	97.178				
14	.229	1.526	98.704				
15	.194	1.296	100.000				

To select items for subscales, Morrison's et al.'s (2000) criteria were applied: factor loading > 0.3 and clear superiority (difference > .01) in loading on one factor rather than the other.

Table 3.2: Structure matrix of factor analysis for this study and Morrison et al.'s (2000).

Item		**This study**		**Morrison's**	
		Factor 1	**Factor 2**	**Factor 1**	**Factor 2**
1	A passing thought will seem so real that it frightens me.	.62	.44	.51	.42
2	My thoughts seem as real as actual events in my life.	.53	.63	.28	.45
3	No matter how much I try to concentrate on my work unrelated thoughts always creep into my mind.	.58	.51	.11	.34
4	I have had the experience of hearing a person's voice and then found that there was no one there.	.34	.36	.63	.39
5	The sounds I hear in my daydreams are generally clear and distinct.	.11	.79	.08	.65
6	The people in my daydreams seem so true to life that I think they are real.	.17	.78	.18	.69
7	In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it.	.33	.65	.06	.62
8	I hear a voice speaking my thoughts aloud.	.35	.53	.33	.54
9	I have been troubled by hearing voices in my head.	.53	.38	.26	.57

10	I have seen a person's face in front of me when no one was there.	.58	.54	.53	-.34
12	I have heard the voice of God speaking to me.	.10	.33	.39	.42
13	When I look at things, they appear strange to me.	.82	.21	.75	.40
14	I see shadows and shapes when there is nothing there.	.71	.27	.65	.34
15	When I look at things, they look unreal to me.	.80	.06	.74	.14
16	When I look at myself in the mirror, I look different.	.719	.206	.64	.16

It is important to note that, at the item level, there are both consistencies and inconsistencies with Morrison et al's findings. For example, item 15 had much higher loadings for the visual factor in both studies (.80 and .74 vs .06 and .14 in this study and Morrison et al. respectively whereas item 9 had a different pattern of loadings in the two studies (.53 and .26 vs .38 vs .57).

To create subscales, items were selected for which the loading were consistent between this study and Morrison et al.'s, yielding two 6 item sub-scales measuring visual and primarily auditory experiences, shown in Table 3.3. For the items measuring visual experiences, the alpha coefficient is .79. For the 6 items sub-scale measuring auditory experiences the alpha coefficient is .74. The Pearson correlation between the visual and auditory hallucination sub-scale was .41, $p < .001$. Figure 3.3 shows the distribution of the auditory scores and Figure 3.4 shows the distribution for the visual scores. Note that the visual subscale is highly skewed, probably reflecting the fact that items measured more severe experiences.

Table 3.3: Visual and auditory sub-scales.

Visual items	**Auditory items**
A passing thought will seem so real that it frightens me.	My thoughts seem as real as actual events in my life.

I have seen a person's face in front of me when no one was there.	The sounds I hear in my daydreams are generally clear and distinct.
When I look at things, they appear strange to me.	The people in my daydreams seem so true to life that I think they are real.
I see shadows and shapes when there is nothing there.	In my daydreams I can hear the sound of a tune almost as clearly as if I were actually listening to it.
When I look at things, they look unreal to me.	I hear a voice speaking my thoughts aloud.
When I look at myself in the mirror, I look different.	I have heard the voice of God speaking to me.

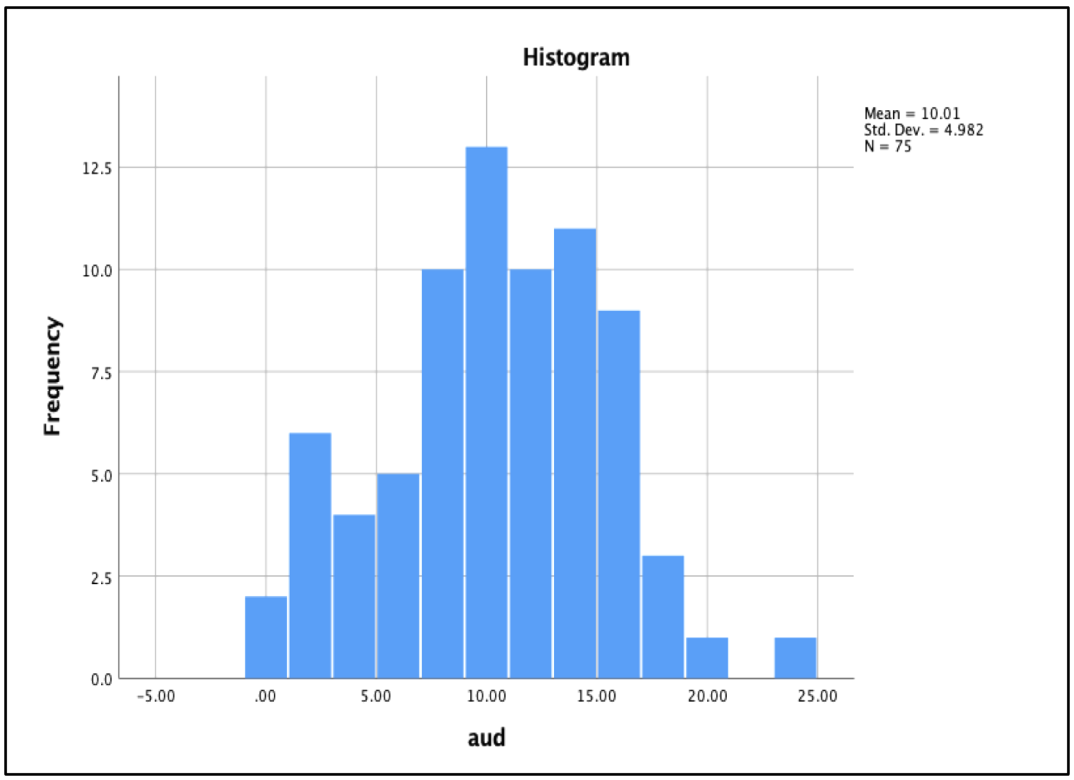

Figure 3.3: Shows sub-scale auditory ($LSHS_{(A)}$) score distribution.

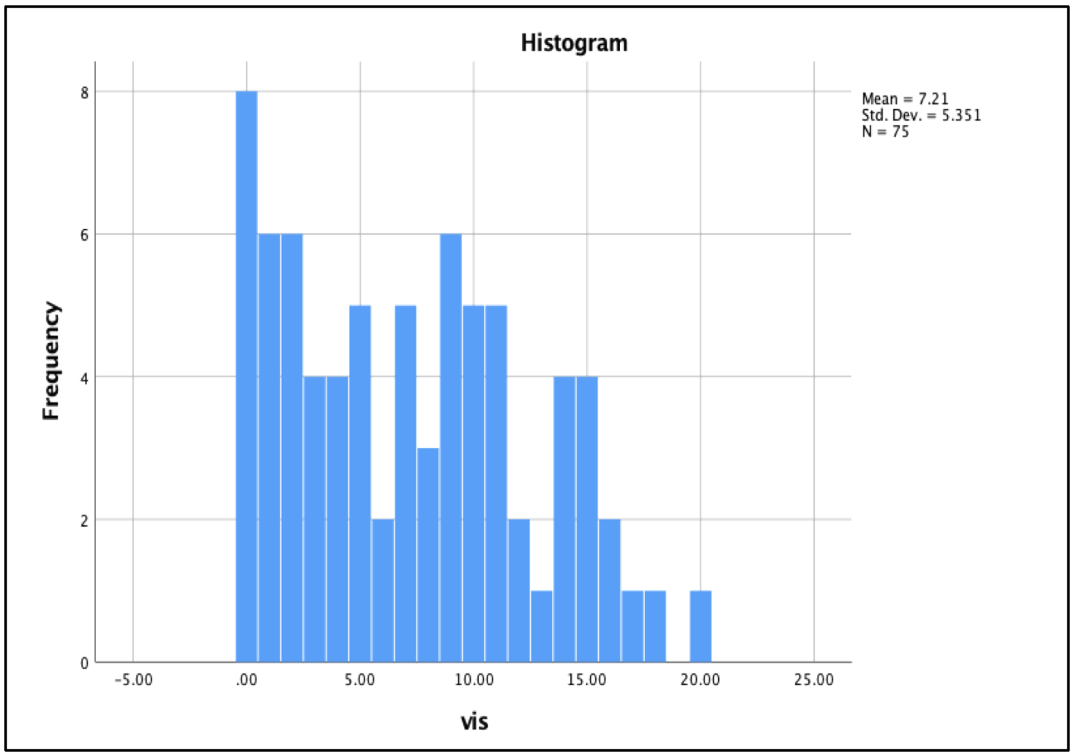

Figure 3.4: Shows sub-scale of visual (LSHS$_{(V)}$) score distribution.

Coefficient alpha for the 8 PaDS persecution items was .76, and for the DES with item 27 removed was .92. The correlation matrix for LSHS$_{(M)}$ total scores, sub-scales scores and the other variables is shown in Table 3.8. A significant positive correlation was found between modified LSHS$_{(M)}$ scale and the DES as expected. Moreover, a significant positive correlation was also observed between auditory (LSHS$_{(A)}$) and visual (LSHS$_{(V)}$) scores and the DES. Surprisingly, and contrary to prediction, the PaDS persecution scale did not correlate with any of the hallucination scores.

Table 3.4: Correlation matrix for modified LSHS$_{(M)}$, sub-scales (visual LSHS$_{(V)}$ & auditory LSHS$_{(A)}$), PaDS and DES.

Correlations	LSHS$_{(M)}$	Visual	Audio	PaDS	DES
LSHS$_{(M)}$					
Visual	.85**				
Audio	.76**	.48**			
PaDS	.22	.14	.24*		
DES	.52**	.44**	.40**	.28*	

** Correlation is significant at the 0.01 level (2-tailed).

* Correlation is significant at the 0.05 level (2-tailed).

3.7 Discussion

In this chapter, I set out to determine the reliability and validity of the modified $LSHS_{(M)}$ scale, to attempt to replicate the factor structure reported by Morrison et al. (2000), to create subscales assessing auditory hallucination proneness and visual hallucination proneness for use in the imaging analysis and to test the validity of both the total scale and the derived subscales against two variables known to be associated with hallucinations: paranoia and dissociation.

The study findings only partially replicated Morrison's et al. (2000). Whereas it was possible to extract two factors corresponding to visual and auditory experiences, inspection of the individual item loading suggests come inconsistency between the two studies. Morrison's study classified 6 items in a sub-scale measuring tendency towards visual hallucination and a 7 items sub-scale measuring tendency towards auditory hallucination. In this study, we selected 6 items in the sub-scale measuring predisposition toward visual hallucination $LSHS_{(V)}$ and six items for the sub-scale measuring predisposition toward auditory hallucination $LSHS_{(A)}$.

Higher amounts of variance were accounted for in this study compared to Morrison et al. (2000). Another encouraging finding was that the reliabilities of the subscales derived in this study were higher than those in Morrison's study (.79 vs .75 for visual hallucinations and .74 vs .64 for verbal hallucinations).

There were differences with respect to the assignment of the items to two sub-scales between Morrison's et al. (20000) and this study. These differences could possibly reflect the sample recruited, as the sample in this study was smaller than the samples in Morrison's et al.'s (2000) study (105 participants), and the ratio of female participants to male participants were different (male: female ratio of this study was 23: 52, while 21: 84 in Morrison's study). However, these differences were not great, and both studies used student samples. Another possibility is that differences between this study and Morrison et al's (and also other previous

factor analytic studies of the LSHS) reflect the severity of hallucinatory experiences indexed by the individual items. In Launay and Slade's (1981) original study, items were selected to fit the Rasch model and so varied in their 'difficulty' (probability of endorsement). Although there were good practical and psychometric reasons for doing this (it would ensure the scale discriminated across a range of disposition towards hallucination) it is notable that, in the present analysis, the more rarely endorsed items belonged to the visual subscale. This is consistent with a research literature which suggests that, in patients, visual hallucinations are associated with greater global severity of psychotic illness (Mueser et al., 1990). An implication is that the ability to distinguish between verbal and visual factors may vary between groups differing in overall severity of hallucination-proneness (at a low level of severity, only verbal items would be endorsed and therefore, in all likelihood, these would dominate the factor structure; at high levels of severity high endorsement of both types of items might again make them difficult to distinguish; therefore it is in the middle range that the two types of experiences are most likely to be evident in the factor structure).

The evidence regarding the validity of the total scale scores and subscale scores was mixed. Surprisingly, in this study there was no correlation between the modified $LSHS_{(M)}$ or its sub-scales with paranoia; this is inconsistent with literature showing a positive syndrome of psychosis (van Os and Kapur, 2009) and with past research with schizotypy scales (e.g. Bentall et al. 1989). On the other hand, this study did find significant positive correlations between modified $LSHS_{(M)}$ scale and the sub-scales with the DES, which is consistent with previous studies (Pilton et al. 2016).

3.8 Limitations

Several limitations of the present study should be noted. First, the sample size was modest and consisted mainly of students; it would be useful to replicate the present findings in a larger more representative sample and also compare factor structures in samples that have been preselected on a criterion for severity of psychosis proneness. Second, the Launay-Slde scale was administered online, although when internet-administered and conventionally

completed questionnaires are compared results are usually similar (Ritter, Lorig, Laurent & Matthews, 2004).

3.8 Conclusion

This study assessed the reliability and factor structure of the modified $LSHS_{(M)}$. Although the findings were not entirely consistent with previous research, two reliable subscales corresponding to verbal and visual hallucinatory experiences were derived. These subscales will be used in the imaging analyses reported in later chapters.

Chapter 4

4.1 Links Between Hallucination Proneness and Brain Morphology

The reported lifetime prevalence of hallucination in the general population is surprisingly high at around 7.3% (random sample n=2533, Kråkvik et al., 2015) to 9.6% (meta-analysis, Maijer et al., 2018). Reviews of incidence studies suggest rates of new hallucinatory experiences are much lower at around 0.5% per year (based on two 5000+ population cohorts, NEMESIS and NEMESIS-2, Moriyama et al., 2020). Only 16% of those who experienced AVH in the general population sought professional help for these experiences (Kråkvik et al., 2015).

Hallucinations are common in psychiatric (schizophrenia: 60-80% incidence) or Parkinson's patients (42% incidence, Wu et al., 2016). Hallucinations are at the core of the diagnosis of schizophrenia and schizoaffective disorders: Baethge et al. (2017), for example, show that 36.6% of schizophrenia patients report hallucinations on admission and argue that the experience is as a sign of the severity of acute illness.

Lifetime prevalence rates in the patient population are much higher at around 70% for auditory, 10% visual, 16% tactile and 9% olfactory/gustatory experiences (data averaged from Mueser et al., 1990, and McCarthy-Jones et al., 2017). This, however, should not detract from the finding that the lifetime prevalence of hallucination in the general population is more than three times that of the lifetime prevalence of all psychotic disorders (3.06%) and more than ten times higher than the prevalence of schizophrenia (0.87%), the disorder with the strongest link to hallucinations (Perälä et al., 2007). Consistent with this, Moriyama et al. (2020) show that the annual incidence of hallucinatory experiences in healthy people is roughly 25 times higher than the reported incidence of psychotic disorders (0.02%). Only 16% of those who experienced AVH in the general population sought professional help for these experiences, Rollins et al. (2019).

In combination, the lifetime prevalence and annual incidence data show that hallucinations, while being unusual experiences, are not uncommon and are significantly more commonly experienced by *healthy* individuals than by those with mental health issues.

Baumeister et al. (2017) in a systematic review examined how voice hearers in the clinical population related to those in the healthy population. They highlight similar risk factors

(familiar and childhood trauma) and subjective perceptual experiences of voices in clinical and non-clinical groups; that healthy voice-hearers hear voices less frequently, with less negative content, with more perceived control and from an earlier age; and that both groups differ in beliefs about voices, voice-related distress, and affective difficulties. Healthy voice-hearers show more cognitive biases, psychiatric symptoms and functional impairments than healthy controls.

The finding that hallucinatory experiences are not necessarily a symptom of mental illness and share significant characteristics across clinical and non-clinical groups has led to marked shift from categorical, diagnostic models towards a continuum-view of psychotic symptoms and anomalous experiences that extends into the healthy general population (Claridge, 1994; Bentall, 2003).

4.1.1 Hallucination other than AVH

While auditory-verbal hallucinations are most common (lifetime prevalence 64–80%), similar experiences area reported in other sensory modalities. McCarthy-Jones et al. (2016) assessed the prevalence and co-occurrence of hallucinations across the auditory, visual, olfactory, and tactile modalities, in a large sample diagnosed with chronic schizophrenia-spectrum disorders. In addition to auditory hallucinations, visual hallucinations were also experienced in 23–31% of the population. In the majority of cases hallucinations were restricted to a single modality, nearly always AVH. Bimodal hallucinations were experienced by one third of the sample, most commonly AVH and visual hallucination (VH). The most interesting finding of the study was that, while only a minority (30–37%) of patients with lifetime AVH had experienced VH, the vast majority of VH experiences (83–97%) were in patients that had also experienced AVH. VH, therefore, while being reasonably common almost always seem to co-occur with AVH.

With this background it is perhaps not surprising that similar cortical structural abnormalities have been reported for VH and AVH. While simple visual hallucinations are most commonly linked to (visual) striate and extrastriate cortex, more complex hallucinations are tied to areas such as the temporal cortex (Billock, 2016; Zmigrod., 2016). However, there is a limited

number of studies that investigate the structure of VH (Kubera et al., 2019), and the number shrinks further when we specify studies that investigate the structure of auditory and visual hallucination in healthy people (Allen et al., 2008). These studies focus on the areas involved in VH; these are principally the inferior frontal gyrus (IFG) and left frontal gyrus (Gama et al., 2014), or hippocampus (Amad et al., 2014).

4.1.2 Hallucinations in different patient groups: Schizophrenia vs Neurodegeneration

Schizophrenia patients commonly report auditory verbal hallucinations (AVH); this symptom has been linked to systematic abnormalities in brain structure that not only distinguish patients that experience hallucinations from those that don't, but also link specific brain areas to the different hallucinations experienced by different patient groups. Rollins et al. (2019), for example, distinguish between psychiatric patients and those that suffer from Parkinson's disease in a meta-analysis. The data they review shows that psychiatric patients who experience hallucinations, exhibit grey matter reductions in the left insula, anterior cingulate/paracingulate gyrus, and middle temporal gyrus, as well as right inferior frontal gyrus. The same patients show more grey matter in the bilateral fusiform gyrus. Patients with Parkinson's disease, a neurodegenerative disorder that also leads to hallucinations, show GM decreases in different areas: the left lingual gyrus, parahippocampal gyrus, and fusiform gyrus, as well as the right supramarginal gyrus/parietal operculum, thalamus, and lateral occipital gyrus (Rollins et al., 2019). The distinct patterns of neuroanatomic alteration for patients with psychiatric and degenerative diseases, who also experience qualitatively different hallucinations, suggests that there is not a single cause for the experience of hallucinations, instead that a plurality, but consistent anatomical changes may underlie different hallucinatory experiences.

4.1.3 Hallucinations in the Healthy Population – Continuum Theories

The finding that healthy individuals experience hallucinations (healthy voice hearers, HVH) without the need for care and do not appear to suffer the significant distress that hallucinations cause in the clinical populations (clinical voice-hearers, CVH) has led to

significant interest and the proposal of continuum models of psychosis (review, Baumeister et al., 2017). These models posit that, rather than treating hallucinations as a diagnostic feature of psychosis, this anomalous experience should be considered as one symptom that extends not just across diagnostic categories but also into the (healthy) general population. Baumeister et al. (2017) proposes three models that each leads to a distinct set of testable hypotheses that are schematically represented below (Figure 4.1):

Model 1: Diagnostic discontinuous model – Here the clinical (CVH, red shading) and healthy (HVH, green shading) hallucinators are two distinct groups, who not only have highly dissimilar hallucinatory experiences, but underlying physiology. In neuroimaging terms this means that one would expect to observe significant experiential, functional and structural differences between the clinical and healthy group. Healthy controls (HC) and the non-clinical population who experience hallucinations, in contrast, should be indistinguishable in neuroimaging terms. Baumeister et al. (2017) argue that the subjective and objective data on hallucinatory experience make this model unlikely.

Model 2: Quasi-dimensional model – this model assumes a continuum between HC and CVH groups where the incidence and severity of hallucinatory experience (blue shading) gradually increases in the population. The occurrence of psychotic experiences (red shading) is proportional to the distress/need for care. In neuroimaging terms, the model predicts that any consistent structural or functional alterations that are seen in the CVH group should also be present, although possibly in an attenuated form, in the HVH group. The HC and HVH groups are not distinct groups, but hallucinatory experience and functional or structural brain parameters should be correlated.

Model 3: Fully Dimensional Mode – The key difference between models 2 and 3 is that, where model 2 posits that distress/need for care emerge from the degree of hallucinatory experience, model 3 suggests that distress is not related to the degree of hallucinatory experience. In neuroimaging terms model three predicts a shared continuum between hallucinatory experience and brain structure/function but that a separate, possibly physiological, factor leads to psychosis. One would therefore expect to see some correlation of brain structure and hallucinatory experience across all three groups, but

a consistent difference between HVH and CVH groups that is unrelated to hallucination proneness.

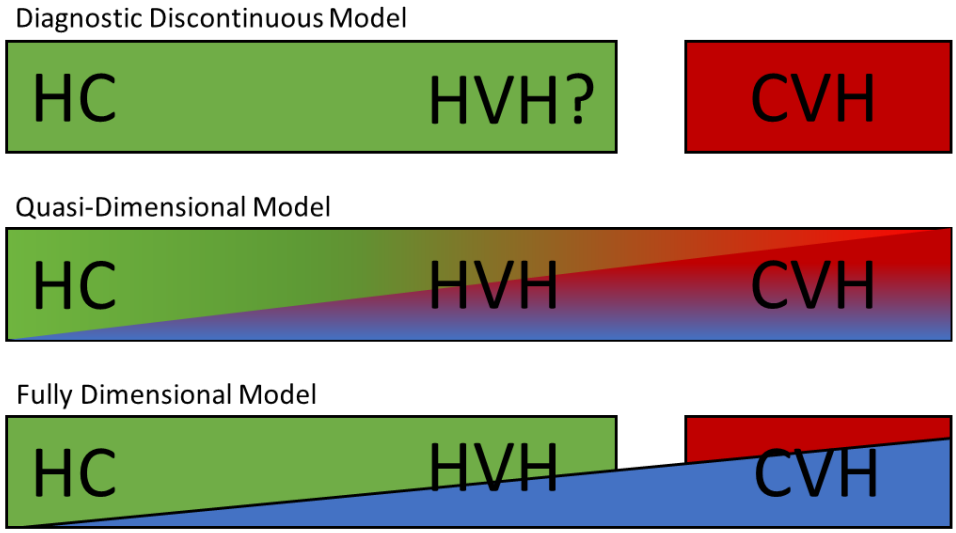

Figure 4.1: Schematic diagram of the three models proposed by Baumeister et al. (2017).

The three groups: healthy controls (HC), healthy (HVH) and clinical (CVH) populations experiencing hallucinations, can either fall into separate groups (model 1) or experience a continuum of hallucinations (models 2 and 3). The difference between the fully and quasi-dimensional model is that the former (model 3) posits that distress and care need are a separate dimension from hallucination incidence, while for the latter model care need is proportional to the frequency and severity of experienced hallucinations. Each of the models leads to a distinct set of testable hypotheses that are discussed in the main text.

General Approach:

While relatively little is known about the link between hallucination proneness and parameters defining brain structure and function in the healthy population, there is a significant literature linking structural brain alterations in the clinical population to hallucinatory experience (Appendix B1). The three models proposed by Baumeister's (2017) provide a theoretical framework with testable hypotheses, that predict brain structural alterations in the HVH group from existing data in the CVH group. Baumeister's quasi-dimensional model, for example, posits that hallucinatory experience and the distress caused by the experience lies on a continuum that ranges from healthy people, who never

experienced hallucinations, via an intermediate group, who experience hallucinations without adverse effects, to psychotic patients. If extreme forms of hallucinatory experience and the need for care are caused by structural brain alterations, then the same alterations should be visible, to a lesser extent, in healthy hallucinators. The model also predicts that there should not be distinct groups, but a continuous range of subjective experience and (correlated) objective measurable alterations to brain structure. The fully dimensional model, which essentially explains the difference between healthy and voice hearers by additional systemic causes that are independent from the causes of hallucinations, suggests that, while there is a common basis for hallucinations, for example alterations to cortical structure or function, this by itself does not explain the distinction between healthy and clinical voice hearers. One would therefore expect to see additional functional or structural brain alterations that distinguish both groups.

4.1.4 Linking brain structure to hallucination proneness.

The morphology of cortical grey matter is commonly assessed using T1-weighted MRI together with automated computerised methods that fall into two broad groups: voxel based, volumetric analysis (exemplified by VBM, which is part of the SPM package (Ashburner and Friston, 2000; Wright et al., 1995) and automated surface extraction algorithms, for example FreeSurfer (http://surfer.nmr.mgh.harvard.edu/fswiki/). The two approaches complement each other. Systematic evaluations (Seiger et al., 2018) have shown that, while each technique reliably identifies atrophic brain areas and shows excellent test-retest variability scores, they do result in systematic differences in absolute volumetric estimates. The data generated by the two techniques also are fundamentally different VBM generates parametric maps in a standard space that shows clusters of voxels while FreeSurfer estimates mean structural parameters, such as surface area, volume or thickness for sets of predefined brain areas.

VBM typically transforms individual T1 MRI scans into a common space, individual voxels in this space, after intensity correction and segmentation into grey (GM) and white matter (WM) and cerebrospinal fluid (CSF), represent the proportion of the corresponding tissue in that voxel. Voxel-wise comparisons can be made using the well established SPM analysis pipelines, for example for group comparisons or regression analyses, that result in cluster estimates in

normalised space. These clusters provide a good basis for meta-analyses because they can easily be pooled across studies (Palaniyappan et al., 2012; Mondino et al., 2013; Rollins et al., 2019). VBM studies have identified grey matter differences associated with normal aging, navigation, arithmetic, linguistic and musical learning abilities (Good et al., 2001; Maguire et al., 2000; Mechelli et al., 2004; Sluming et al., 2002).

A commonly used alternative to VBM are tools that reconstruct precise models of the surface separating grey matter from white matter and the pial surface, which separates grey matter and pia mater in the brain. FreeSurfer (http://surfer.nmr.mgh.harvard.edu/fswiki/) is a commonly used example. The software extracts surfaces geometry and automatically parcellates individual brains in native space into cortical areas and computes statistics, such as volume, average thickness, or curvature indices. FressSurfer, like VBM, has been used for many standard applications, such as a measuring grey matter differences associated with normal aging, navigation, language and musical learning abilities (Schmidt-wilcke et al, 2018, Wenger et al, 2012; Martensson et al., 2012, Bailey et al., 2014).

Each of the two approaches has strengths and weaknesses: The voxel based analysis of VBM means that volumetric alterations can be identified for individual voxels, while FreeSurfer computes detailed average statistics for brain areas that can be automatically segmented. VBM uses a volume (voxel space) representation while FreeSurfer extracts the statistics after surface extraction. This means that VBM can detect local volumetric alterations withing large brain structures, such as the inferior, middle and superior temporal gyri, which might be difficult to detect with FreeSurfer because the descriptive averages are computed over large brains areas. FreeSurfer, on the other hand, can attribute fine alterations to individual (adjacent) gyri, which would not be possible with VBM because of the spatial smoothing used in the normalisation of the imaging data. VBM provides the basis for a volumetric comparison while FreeSurfer provides more detailed descriptors of the surface shapes (area, thickness, curvature etc.).

Since the two most commonly used imaging techniques, VBM and FreeSurfer, are complementary, provide slightly different data sets linking hallucination in patients with structural alterations, and are used differently in meta-analyses, we discuss them in turn below.

4.1.5 Voxel Based Morphometry and Hallucination Proneness in Patients

Results from individual voxel-based morphometry studies can be combined in meta-analyses, since the algorithms provide cluster locations of significant alterations in a common space. These analyses can substantially increase the number of 'participants' and avoid biases that are due to sampling effects in relatively small cohorts. The focus of this section will therefore be three meta-analyses that describe brain volume alteration in patients that experience auditory hallucinations relative to a (mostly patient without hallucinatory experience) a control group. The three meta-analyses that form the basis of this review cover data on between 240 to 463 participants. A drawback of the approach is that the meta-analyses combine data across a range of different scanners, scanning parameters and draw on slightly different patient groups (Palaniyappan, 2012 and Modinos et al., 2013: schizophrenia alone, Rollins et al., 2019: schizophrenia and bipolar disorder). Similarly, control groups are mostly patients that do not experience hallucinations, while Modinos et al. (2013) includes a number of studies that draw on healthy controls.

Palaniyappan et al. (2012) conducted a voxel-based meta-analysis of seven studies with 350 patients to link brain structure with auditory hallucinations in schizophrenia. The authors showed a significant negative correlation between the severity of hallucinations and grey matter volume in the left insula and right superior temporal gyrus. Modinos et al. (2013), using a partially overlapping dataset, present a random-effects parametric voxel-based meta-analysis, also linking hallucination severity to grey matter reductions. They identified the bilateral superior temporal gyrus (including Heschl's gyri) as key areas of structural pathology in AVH in schizophrenia. Rollins et al. (2019) considered patients with psychiatric and neurodegenerative diseases in their meta-analysis. Their principal finding, as discussed above, was that different patient groups exhibit different neurological alterations, for schizophrenia patients Rollins et al. (2019) show that patients with psychiatric disorders and hallucinations are characterised by reduced grey matter in the left insula, right inferior frontal gyrus, left anterior cingulate/paracingulate gyrus, left middle temporal gyrus, and increased grey matter volume in the bilateral fusiform gyrus. Diametrally opposite findings were presented by Zhuo et al. (2020) for healthy individuals with AVH (H-AVH). They showed enlarged temporal lobe grey matter volume in H-AVH subjects compared to healthy controls without AVH, and

therefore argue that increased grey matter volume in temporal areas reflects pathological features of AVH, consistent with the hypotheses that temporal lobe hyperactivity may be an intrinsic feature of AVH symptomology (Curcic-Blake et al. 2017; Hugdahl 2015; Kompus et al. 2011; Morch-Johnsen et al. 2017; Steinmann et al. 2014; Upthegrove et al. 2016; van Lutterveld et al. 2014; Wigand et al. 2015).

The changes, which are broadly consistent in the three studies, are shown diagrammatically in Figure 4.2, they identify volume reductions in brain areas that are functionally associated with language or auditory processing.

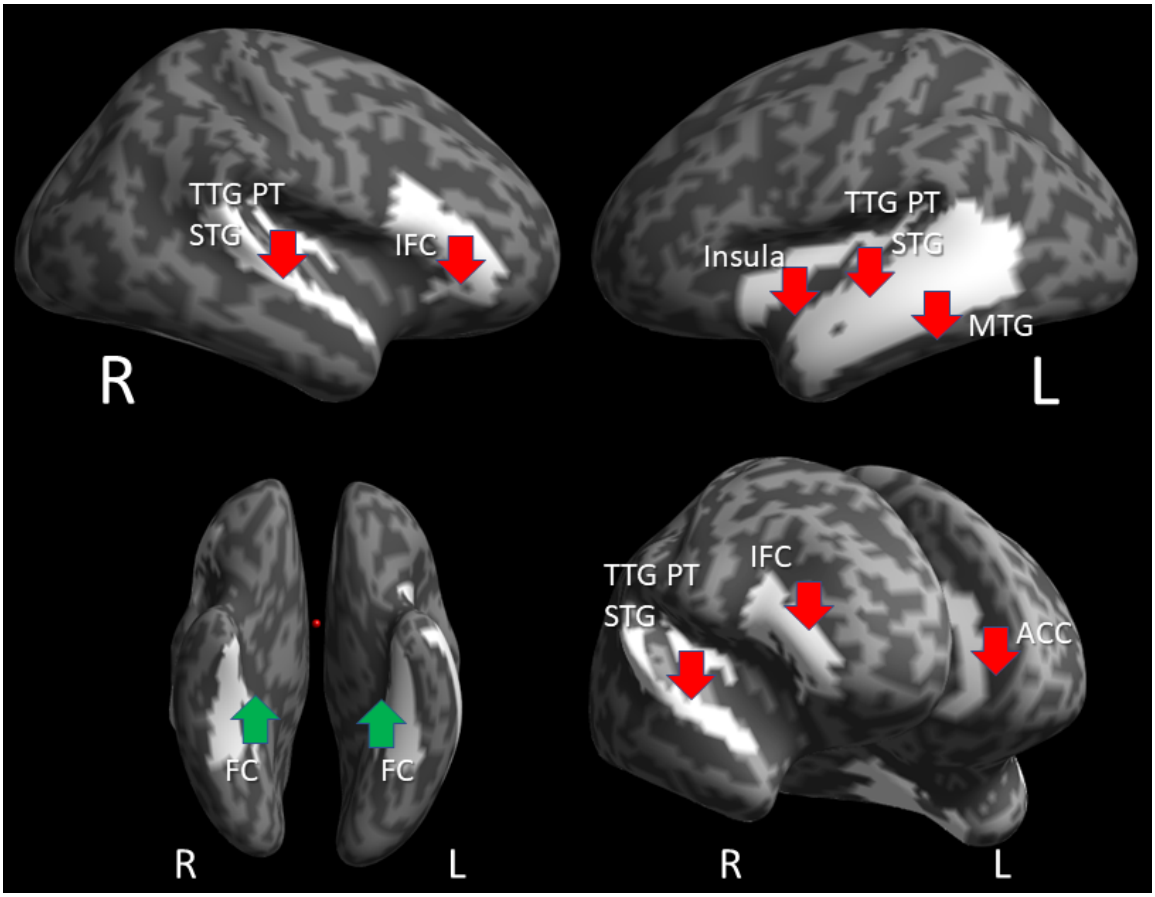

Figure 4.2: Schematic diagram of volumetric brain alterations identified in three meta analyses in clinical populations suffering from hallucinations. Red arrows indicate volumetric reductions observed in Insula, TTG, PT, STG MTG and IFC, green arrows indicate volume increases in FC.

4.1.6 Summary of Areas linked to Hallucination Proneness using Voxel-wise studies

Table 4.2 shows previous studies investigate the structure change in the AVH patients through using voxel-wise volumetric density measurements. It is reported reduction in the areas related to the AVH.

Table 4.1: Voxel-wise studies comparing volumetric differences between patients experiencing auditory verbal hallucination (AVH) with control groups.

Authors	Subjects	Structures alteration
Van Tol., 2014	65 AVH patients 44 Non-AVH patients	AVH patients ↓ volume in LT STG, LT IFG, RT parahippocampal gyrus.
Nenadic., 2010b	38 AVH patients 61 Non-AVH patients	Bilateral STG, LT Supramarginal/angular gyrus, LT postcentral gyrus and LT posterior cingulate cortex.
Modinos., 2009	26 schizophrenia patients	LT IFG, LT STG, LT MTG, RT IFG, hippocampus and insula volumes positive correlated with hallucination severity.
Garcia-Mari., 2008	18 AVH patients 19 healthy	AVH patients ↓ insula, STG, LT amygdala.
O'Daly., 2007	28 AVH patients 32 healthy control	AVH patients ↓ volume RT STG, insula.
Neckelmann., 2006	12 AVH patients 12 healthy	AVH patients ↓ volume LT STG, LT MFG, RT cuneus.
Gaser., 2004	29 AVH patients 50 Non-AVH patients	AVH patients ↓ volume RT MFG, IFG, LT TTG, LT supramarginal gyrus.
Shapleske., 2002	41 AVH patients 31 Non-AVH patients	AVH patients ↓ volume insula, MTG, anterior cingulate, Precuneus.
Tang et al., 2012	29 AVH patients 34 control	AVH patients ↓ volume LT STG and MTG.
Escarti et al., 2019	93 AVH patients 122 Non-AVH patients	AVH patients ↓ STG, MTG, IFG and Insula.

Key: AVH: auditory verbal hallucination, Non-AVH: non auditory verbal hallucination, ↓: decrease, LT: left, STG: superior temporal gyrus, RT: right, IFG: inferior frontal gyrus, MTG: middle temporal gyrus, MFG: middle frontal gyrus, TTG: transverse temporal gyrus.

4.1.7 Surface Based Morphometry and Hallucination Proneness in Patients

A number of studies, some using quite large sample sizes, investigated the link between surface statistics and hallucinatory experiences. In contrast to voxel-based studies where the centres of significant clusters can be used for meta-analyses, this is not possible for surface statistical analyses unless the raw data is available. Table 4.3, consequently, shows a summary of previous research findings.

Table 4. 2: Surface Based Morphometry studies.

Authors	Subjects	Structures alteration
Chen et al., 2015	18 AVH patients 31 Non-AVH patients	RT Heschl's gyrus ↓ thickness in AVH patients
Cui et al., 2017	115 AVH patients 93 Non-AVH patients	LT MTG ↓ thickness in AVH patients
Van Lutterveld., 2014	27 AVH patients 24 Non-AVH patients	(LT paracentral cortex, LT pars orbitalis, RT fusiform gyrus, RT ITG, RT insula) ↓ thickness in AVH patients
Kubera., 2014	10 AVH patients 10 Non-AVH patient	(MFG, IFG, STG, insula, IPL, TTG, fusiform, MTG, ITG) ↓ volume in AVH patients
Morch-Johnsen., 2017	145 AVH patients 49 Non-AVH patients	LT Heschl's gyrus ↓ thickness in AVH patients
Oertel-Knochel., 2013	25 Schizophrenia 37 control	(Bilateral Heschl's gyrus, LT ITG, RT MTG) ↓ thickness in AVH patients
Kuperberg et al., 2003	33 AVH patients 32 Control	(IFG, STG, MTG and Fusiform) ↓ thickness in AVH patients
Jung et al., 2019	94 AVH patients 52 control	(Fusiform and TTG) volume negative correlation with hallucination severity in patients.

Key: AVH: auditory verbal hallucination, Non-AVH: non auditory verbal hallucination, RT: right, LT: left, ↓: decrease, MTG: middle temporal gyrus, TTG: transverse temporal gyrus, ITG: inferior temporal gyrus and MFG: middle frontal gyrus.

In the Surface Based Morphometry (FreeSurfer) section, the study restricted to analyses regions of interest (ROI) on areas approved related to hallucination in literature Figure 4.3. The ROI are (bilateral TTG, bilateral STG, bilateral MTG, bilateral ITG, bilateral IFG, bilateral MFG, bilateral Fusiform, bilateral Insula, bilateral lingual, bilateral Supramarginal, bilateral Precuneus and bilateral cuneus) thickness and volume.

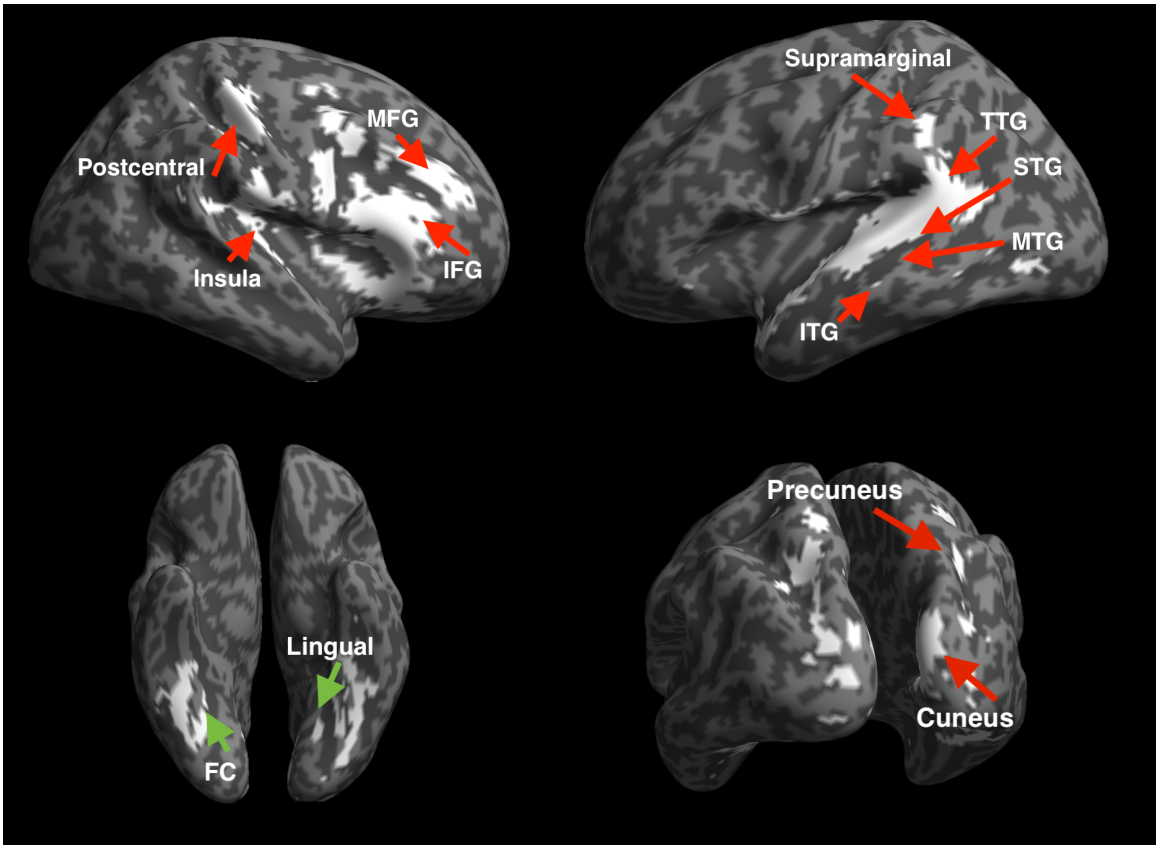

Figure 4.3: Schematic diagram of brain regions alteration in previous studies comparing patient with control. {ABDULLAH} Red arrows indicate volumetric reductions observed in Insula, TTG, PT, STG MTG and IFC, green arrows indicate volume increases in FC. < don't use this text, but add the relevant regions – we discussed the arrows, I made them point up or down to indicate how VBM data changes, in Figure 4.2 they are NOT pointing from the label to the area.

4.1.8 Quantifying hallucinatory Experience

The Launay-Slade Hallucination Scale (LSHS) (Launay & Slade., 1981) is a reliable tool for measuring hallucination proneness in clinical and non-clinical subjects (Castiajo & Pinheiro., 2017). This 12-item revised scale is commonly used in hallucination studies (R. P. Bentall & Slade., 1985). In the current study, as part of the process of recruiting my participants, (Morrison's et al, 2000) Launay-Slade Hallucination Scale Modified ($LSHS_{(M)}$) used to recruit participants. In addition, $LSHS_{(A)}$ and $LSHS_{(V)}$ used for correlation with brain structures. More details about the $LSHS_{(M)}$ questionnaire are available in Chapter 3.

The pattern of associations with other variables and between different modalities was similar for self-reported and clinically validated measures, suggesting self-reported measures of hallucinatory experiences are valid, as reported in previous studies examining this issue (Bak et al., 2003; Kelleher et al., 2011; van der Steen et al., 2017; van Nierop et al., 2012).

4.1.9 Hypotheses

The continuum hypothesis states that hallucinatory experiences in the healthy group and in patients have a common cause – the severity of experience or an additional factor determines whether hallucinations require clinical attention.

The hypothesis we test, consequently is that hallucination proneness measures, here the $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ scales, predict cortical structural alterations that have been described for patients in the healthy population. Volumetric or surface statistics should be correlated with the $LSHS_{(M)}$ scores.

First, CAT12 region of interest (ROI) will be correlated with the $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$. Moreover, CAT12 whole brain analysis will conduct by using $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ as a regressor. I expect to found negative correlation between $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ with TTG, STG, MTG, IFG, MFG and Insula.

Second, the ROI in FreeSurfer analysis will correlate with $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$. This study expects the correlation with the $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ will be significantly negative in the areas related to the auditory and visual hallucination in CAT12 and FreeSurfer (TTG, STG, MTG, IFG, MFG, Insula and Fusiform).

4.2 Methodology

The study was conducted in the Liverpool Magnetic Resonance Imaging Centre (LiMRIC) at the University of Liverpool, and it was approved by the University ethics committee (ref IPHS-1516-LB-128). All participants gave informed, written consent.

4.2.1 Participants

To gather undiagnosed participants, I used the Qualtrics website to create a link to $LSHS_{(M)}$. The Qualtrics link was distributed across the university, via email, and posters in the libraries. Participants diagnosed with AVH excluded up-front Seventy-five participants completed the $LSHS_{(M)}$ questionnaire online. All undiagnosed participants were then invited to undergo an MRI scan. Seventy-five participants agreed to involve in the MRI study and answered another two questionnaires Dissociative Experience Scale (DES) and Persecution and Deservedness (PaDS3). Sixth participants excluded because they had metal implants such are piercing. Only sixty-nine participants, all of whom were either university students or staff, agreed to the MRI scan. After the scan, one participant was excluded because of an abnormal finding. Therefore, the study was performed on sixty-eight undiagnosed participants; twenty-sixth were male and forty-two were female, with an average age of 29.1 years (Standard Deviation [SD]=11.956; range,19-66).

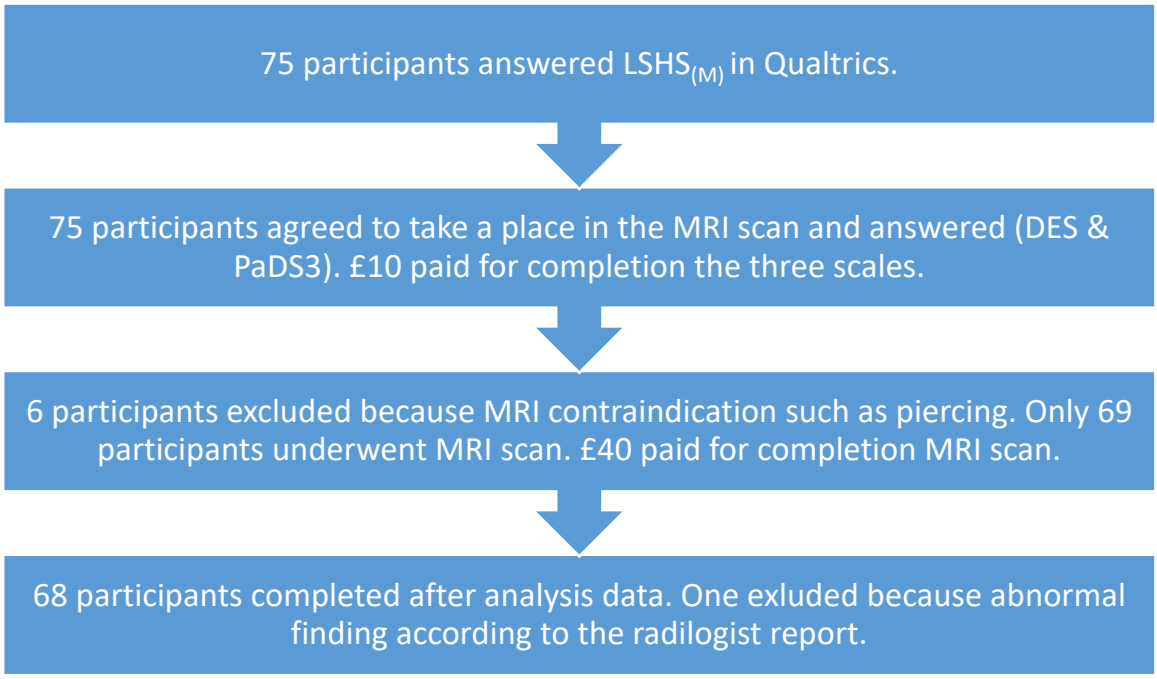

Figure 4.4: Schematic diagram explaining the recruitment process.

4.2.2 Parameters

A Siemens MAGNETOM Prisma 3T MRI scanner was used in this study. The magnetisation-prepared radio-frequency pulses and rapid gradient-echo (MPRAGE) sequence was used to take 3D T1 sagittal images. This sequence is used for research and clinical purposes. The parameters were: voxel size 1.0 x 1.0 x 1.0 mm; TR 2000.0 ms; TE 2.25 ms; FoV read 224 mm; flip angle 8 deg.

4.2.2.1 CAT12 Preprocessing

The CAT12 software was used to analyse the 3D T1 images. CAT12.5 (r1363) from 02/09/2018 was the version used to analyse the data; this version can run within the statistical parametric mapping software SPM12. CAT12 provides good normalisation and segmentation methods; moreover, it gives improved detection of volumetric alteration (Farokhian, Beheshti, Sone, & Matsuda, 2017). Through Exponentiated Lie DARTEL registration template was used, and again the default parameters were used. DARTEL is a method used CAT12 to promote the correct realignment of small subcortical structures and has been shown to be more sensitive to regional changes in brain volume the standard CAT12 method (Farokhian et al., 2017). In order to display the results and precise their anatomical location we used an additional SPM extension, WFU_PickAtlas used to extract regions of interest, the mask based on Talairach Daemon database (https://www.nitrc.org/projects/wfu_pickatlas/). REX is tool in SPM used to extract data from region of interest (https://www.nitrc.org/projects/rex/).

4.2.2.2 FreeSurfer Preprocessing

FreeSurfer v6.0.0 structural MRI analysis software was used to analyse the 3D T1 sagittal images (Fischl, 2012). This software automatically segments and parcellates structural images into cortical and subcortical regions. FreeSurfer converts the image from 3D voxels into a 2D triangular mesh surface that enables the calculation of area, curvature, thickness and volume for each different structure. In addition, Prior publications described the technical details of the FreeSurfer preprocessing procedures (Fischl and Dale, 2000; Dale et al., 1999; Fischl et al, 1999. FreeSurfer allows for parcellation of the cortical area and segmentation of

the subcortical area. GraphPad Prism version 8.4.0 (https://www.graphpad.com) used to correlate the FreeSurfer data with $LSHS_{(M)}$.

4.3 Data Analysis

4.3.1 CAT12 Analysis

The regions related to auditory and visual hallucination extracted and correlated with $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$. Moreover, $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ were used as regressors to carry out a whole brain statistical test. To identify regions where the $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ were used as a covariate to ascertain whether there was any positive or negative correlation between the cortical change. The brain volumes were normalised. Uncorrected threshold $p < 0.001$ used. The regions extracted were bilateral of transverse temporal gyrus (TTG), superior temporal gyrus (STG), middle temporal gyrus (MTG), inferior temporal gyrus (ITG), Insula, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), Fusiform, Supramarginal, Lingual, Postcentral, Planum temporale, Pars orbital and Cingulate. These regions selected according to the previous studies (Figure 4.2), which shows associated with hallucination. WFU_PickAtlas used to extract regions of interest, the mask based on Talairach Daemon database (https://www.nitrc.org/projects/wfu_pickatlas/). REX used to extract the value from mask created (https://www.nitrc.org/projects/rex/).

4.3.2 FreeSurfer data analysis

FreeSurfer performed segmentation based on Deskan-Killiany cortical atlas (https://surfer.nmr.mgh.harvard.edu/fswiki/CorticalParcellation). The brain volumes were normalised. Gray matter common regions (thickness and volume) to hallucinations correlated with $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$. The regions extracted were bilateral of transverse temporal gyrus (TTG), superior temporal gyrus (STG), middle temporal gyrus (MTG), inferior temporal gyrus (ITG), Insula, inferior frontal gyrus (IFG), middle frontal gyrus (MFG), Fusiform, Supramarginal, Lingual and Precuneus. These regions selected according to the previous studies (Figure 4.3), which shows associated with hallucination. GraphPad Prism and Origin both used to perform the correlation. All the volumes brain was normalised.

4.4 Results

4.4.1 CAT 12 result

The data extracted from ROI in CAT12 correlated with $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ and shows no correlation (appendix B1, B2, B3). Moreover, two correlations performed through using $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ as a regressor. First test was a negative correlation performed between the CAT12 and $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ and shows no correlation. However, a positive correlation performed between the whole brain and the $LSHS_{(M)}$ as a regressor (Figure 4.5) and shows a positive correlation with right superior temporal gyrus (RT STG) and extend to right middle temporal gyrus (RT MTG). Furthermore, $LSHS_{(M)}$ shows a positive correlation with right middle occipital gyrus (RT MOG). Moreover, $LSHS_{(M)}$ shows a positive correlation with left middle temporal gyrus (LT MTG). Also, it shows a positive correlation with left middle occipital gyrus (LT MOG). Table 4.3 shows the regions coordinate positively correlated with $LSHS_{(M)}$ scores. $LSHS_{(A)}$ and $LSHS_{(V)}$ used as a regressor, but no correlation found.

Table 4.3: $LSHS_{(M)}$ used as regressor.

Cluster-level				**Coordinates**		
p uncorr	**Hemisphere**	**Anatomical area**	**t**	**x**	**y**	**z**
0.010	rh	Superior temporal gyrus	3.82	54	-36	8
0.186	lh	Middle occipital gyrus	4.14	44	-63	24
0.114	rh	Middle occipital gyrus	4.14	-34	-64	24
0.808	lh	Middle temporal gyrus	3.28	-48	-21	-10

0.010	rh		Middle temporal gyrus	3.76	44	-34	-6

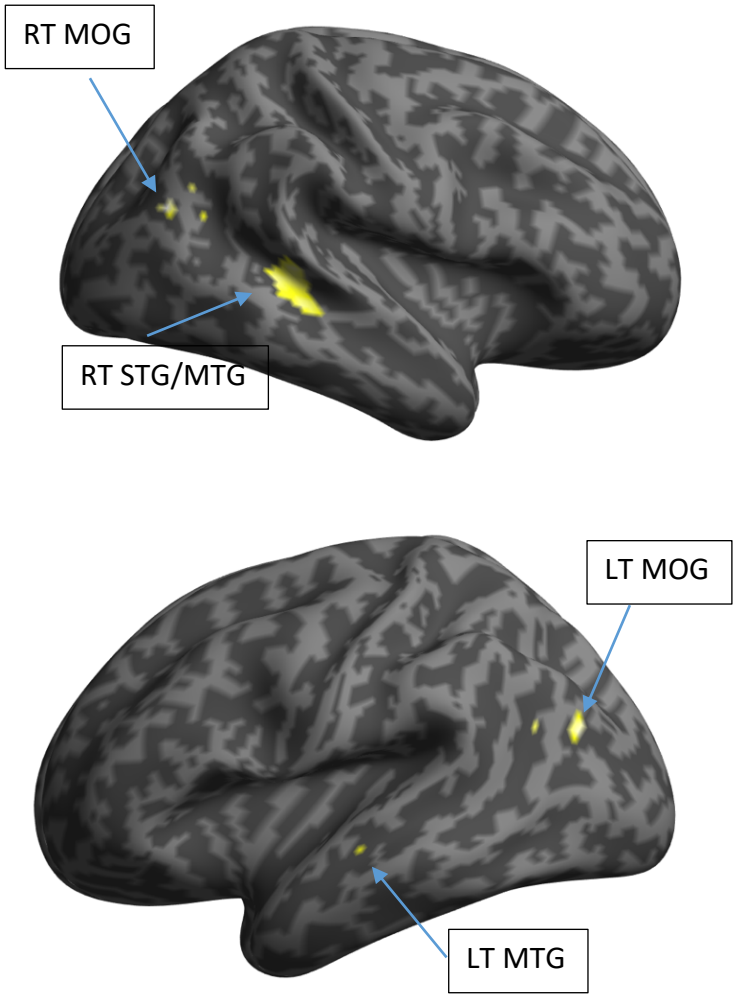

Figure 4.5: LSHS$_{(M)}$ used as a regressor and shows positive correlation bilateral MTG, RT STG and MOG.

4.4.2 FreeSurfer correlation results

4.4.2.1 LSHS$_{(M)}$ Scores vs. Hallucination Areas

Non-parametric tests performed because the structural data did not pass the normality test.

Full results of the correlation analysis are shown in Tables (appendix B4-1). Here only the correlation results for the $LSHS_{(M)}$ score are shown, the other two scores provided comparable data.

As can be seen in Table 4.4, the results show a significant positive correlation between $LSHS_{(M)}$ scores and ROI in hallucination (bilateral TTG thickness, lh MTG thickness, lh MTG volume and lh Fusiform thickness), compared to the results in the previous studies (Chen et al., 2015; Cui et al., 2017).

Table 4.4: Regression coefficients (slope) for $LSHS_{(M)}$ score and specified FreeSurfer metrics in ROI that have previously been related to hallucination. References to the studies reporting differences between patient and controls are given on the left. Where previous work reports a reduction in patients relative to controls a negative slope is expected.

Brain Area Patient Data		**Observed Regression Coefficient $LSHS_{(M)}$**				
			Value	**Standard Error**	**t-Value**	**Prob>|t|**
TTG	Chen et al, 2015; Van Swam et al., 2012; Gaser et al., 2004; Ehrliich et al., 2012. reduction in AVH patients	Slope lh thickness	0.00607	0.00211	2.88081	0.00535*
		Slope rh thickness	0.01071	0.00231	4.64218	0.000016*
STG	Palaniyappan et al. 2012; Van Swam et al. 2012; Oertel-Knochel et al., 2013; Sun et al., 2009. Reduction in AVH patients	Slope lh thickness	0.00232	0.00158	1.46372	0.14802
MTG	Stanfield et al., 2009; Cui et al., 2017; Job et al., 2002; Toshiaki et al., 2004; Reduction in AVH patients	Slope lh volume	39.9593	18.77014	2.12888	0.037*
		Slope lh thickness	0.0034	0.0014	2.3553	0.0214*
ITG	Van Lutterveld et al, 2014; Highly et	Slope lh volume	3.60726	19.85431	0.18169	0.85639

	al.,1999; Toshiaki et al., 2004 Reduction in AVH patients					
Insula	Garcia-Mari et al, 2008; Ford et al., 2005; O'Daly et al., 2007; Haijma et al., 2013; Shapleske et al., 2002. Reduction in AVH patients	Slope lh volume	5.29598	9.36178	0.5657	0.57351
IFG	(Gaser et al, 2004; Garcia-Marti et al.2008; Huang et al., 2015 Reduction in AVH patients) (Modinos et al., 2009 thicker in AVH patients)	Slope lh volume	-9.9534	23.00056	-0.43275	0.66661
MFG	(Oertel-Knochel et al, 2013; Neckelmann et al., 2009; Kubera et al., 2014 Reduction in AVH patients) (Van Swam et al., 2012 increase in AVH patients)	Slope lh volume	0.23127	36.96979	0.00626	0.99503
Fusiform	O'Daly et al, 2007; Goldman et al., 2014; Janzen et al., 2012; Van Lutterveld et al., 2014 reduction in AVH patients	Slope lh thickness	0.00254	0.00117	2.1721	0.03345*
Supramarginal	Kubera et al, 2014; Gaser et al., 2004 reduction in AVH patients	Slope lh volume	7.07898	23.60492	0.29989	0.7652
Lingual gyrus	Watanabe et al, 2013; Goldman et al., 2014; Janzen et al., 2012. reduction in visual hallucination patients	Slope lh volume	4.05181	12.7995	0.31656	0.75258

Postcentral gyrus	Nenadic et al, 2010; Job et al., 2002. showed correlation with AVH severity	Slope lh volume	14.84255	15.80978	0.93882	0.35125
Planum temporale	(Keshavan et al.,1998; Takahashi.,2007. Reduction in AVH patients) (Morch-Johnsen et al., 2017 thicker in AVH patients)	Slope lh thickness	0.00937	0.00421	2.22428	0.02956*
		Slope rh thickness	1.3751	0.0047	0.02871	0.9771
precuneus	Shapleske et al, 2002 reduction in AVH patients	Slope lh thickness	0.00144	0.00128	1.12005	0.26675

Overall, the results showed a positive correlation between $LSHS_{(M)}$ scores and lh MTG volumes ($p<0.03$). Moreover, positive correlation between $LSHS_{(M)}$ and bilateral TTG thickness ($p<0.05$). The scatter plots in Figure 4.6 show a more positive correlation with rh TTG thicknesses ($p<0.01$) than with lh TTG thicknesses ($p<0.05$). Furthermore, the scatter plots in Figure 4.7 show a positive correlation with lh MTG volume ($p<0.05$).

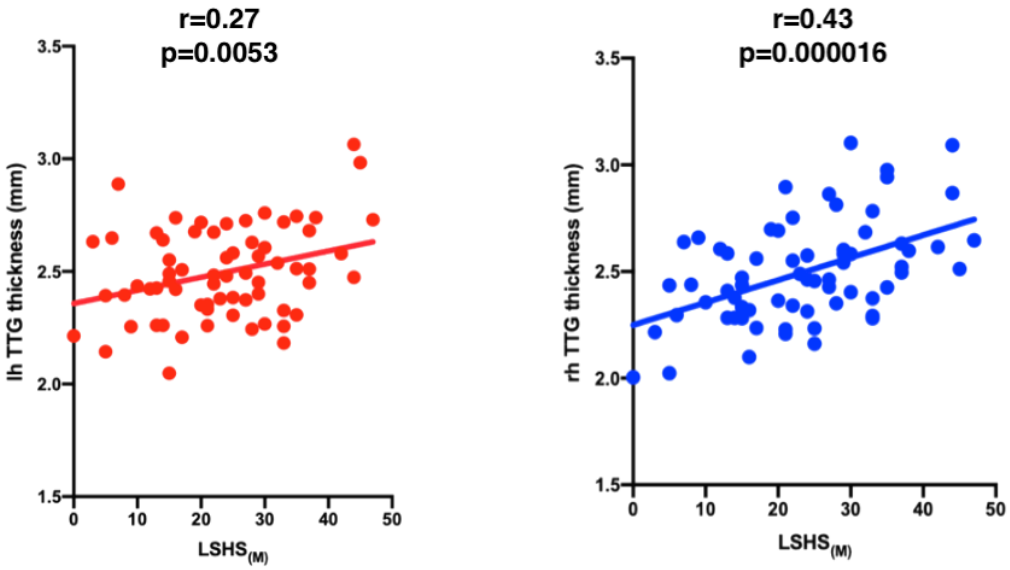

Figure 4.6: Correlation between $LSHS_{(M)}$ scores and lh and rh TTG thicknesses.

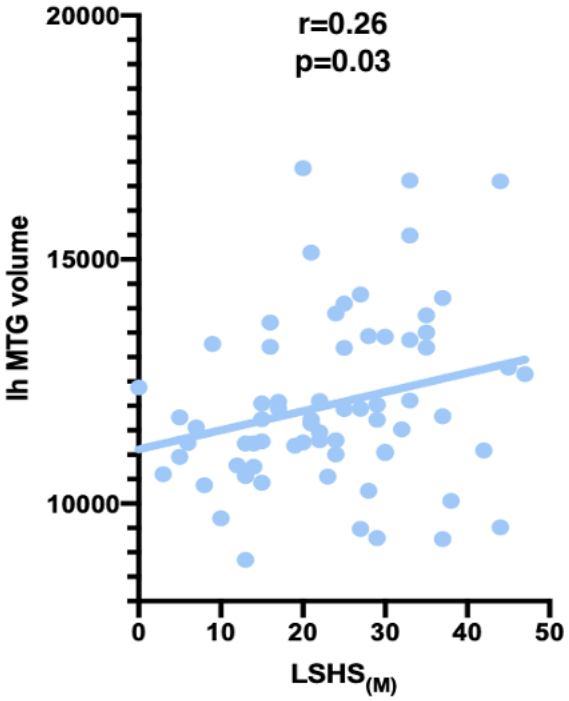

Figure 4.7: Positive correlation between $LSHS_{(M)}$ and left hemisphere volume of middle temporal gyrus.

4.4.2.2 LSHS$_{(A)}$ Scores v Hallucination Areas

A non-parametric test for the correlation between LSHS$_{(A)}$ scores with hallucination areas was carried out (in the appendix B5-1, B5-2, B5-3, B5-4). As can be seen, the result showed that there was a significant positive correlation with bilateral TTG, rh Precuneus, lh Fusiform thickness and LSHS$_{(A)}$. The scatter plots in Figure 4.8 show a positive correlation with bilateral TTG and LSHS$_{(A)}$. The scatter plots in Figure 4.8 show a more positive correlation with rh TTG thicknesses ($p<0.01$) than with lh TTG thicknesses ($p<0.05$). Moreover, the scatter plots in Figure 4.9 show a positive correlation with rh Precuneus and lh Fusiform thickness and LSHS$_{(A)}$. corelation between LSHS$_{(A)}$ score and hallucination area are shown in appendix B4-2.

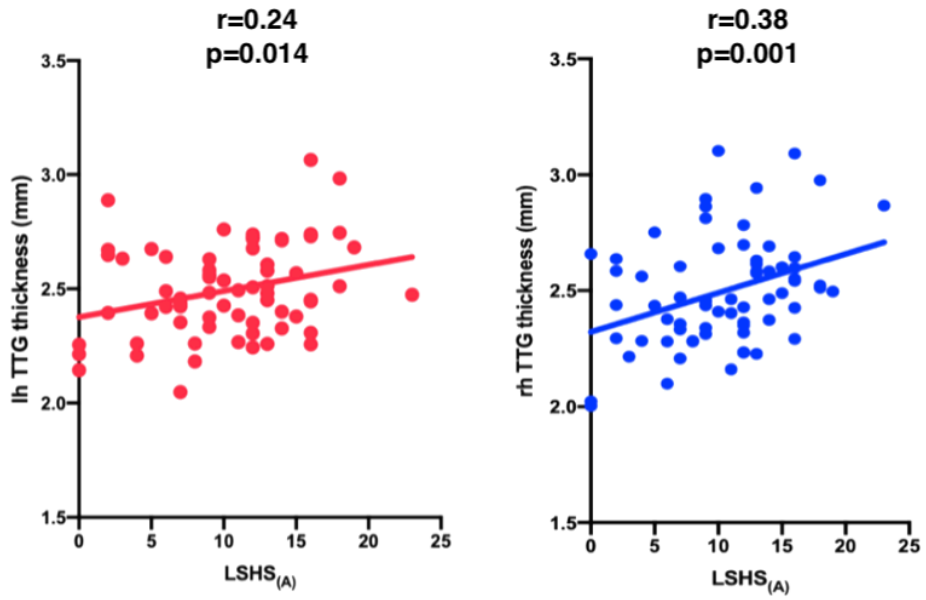

Figure 4.8: Correlation between rh TTG (blue) and lh TTG (red) thicknesses with the LSHS$_{(A)}$ scores.

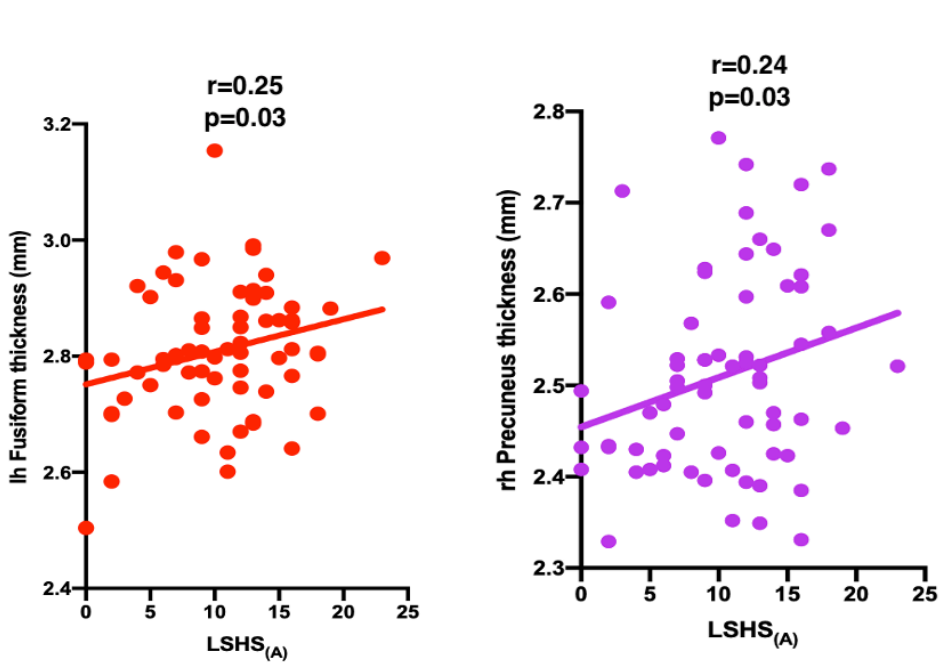

Figure 4.9: Shows positive correlation between $LSHS_{(A)}$ and left hemisphere Fusiform thickness (red). Also, positive correlation between $LSHS_{(A)}$ and right hemisphere Precuneus (purple).

4.4.2.3 $LSHS_{(V)}$ Scores v Hallucination Areas

A non-parametric test was carried out for the correlation between $LSHS_{(V)}$ scores and hallucination areas (in the appendix B6-1, B6-2, B6-3, B6-4). The result showed that there was significant positive correlation with bilateral TTG thickness and lh MTG volume with $LSHS_{(V)}$. The scatter plots in Figure 4.9 show a positive correlation with rh TTG thicknesses ($p<0.01$) with $LSHS_{(V)}$. In addition, the scatter plots in Figure 4.9 show a positive correlation with lh MTG volume with $LSHS_{(V)}$.

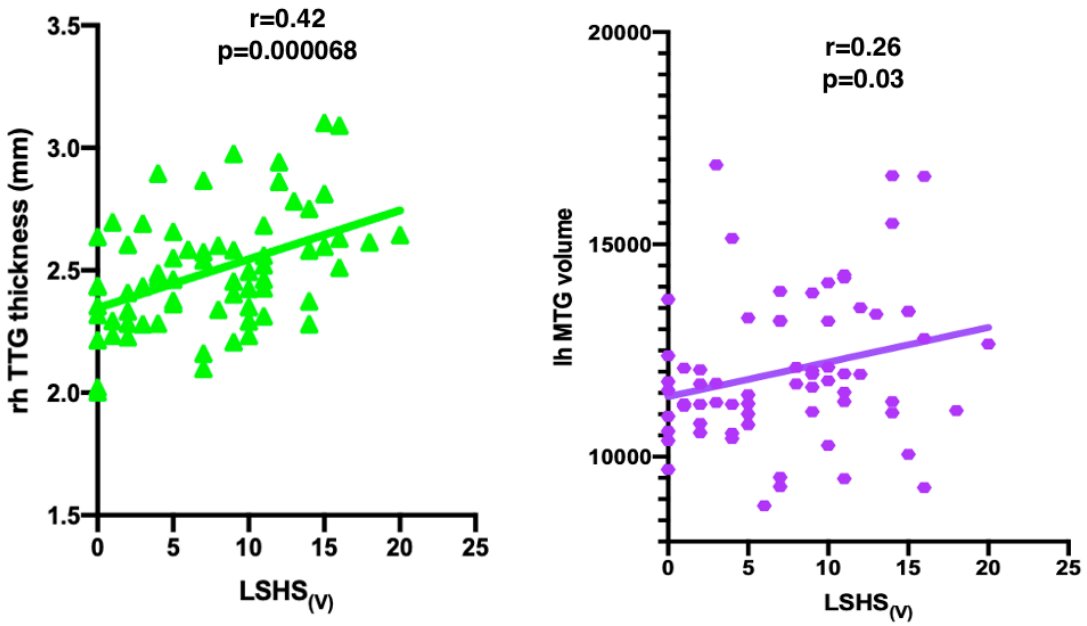

Figure 4.10: This chart shows positive correlation between the $LSHS_{(V)}$ and right hemisphere transverse temporal gyrus (TTG) thickness (green). Furthermore, positive correlation between $LSHS_{(V)}$ and left hemisphere middle temporal gyrus (MTG) volume (purple).

4.5 Discussion

This study tests the continuum hypothesis states that hallucinatory experiences in the healthy group and in patients have a common cause. This means that the volume reductions, which have consistently been reported in language-related areas of patients suffering from hallucinations, should be reflected, possibly in an attenuated fashion, in the healthy population. The specific hypothesis that was tested is that volumetric data from FreeSurfer or VBM analyses should be negatively correlated with ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) hallucination proneness scores.

The principal result of this analysis is that we did not find any significant *negative* correlations between hallucination severity ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and structural measures in either of the two analyses.

The continuum theory places healthy voice-hearers between healthy non-voice-hearers and patients. It might therefore be argued that the sample used in this study did not span the range of hallucinatory experiences. An analysis of the $LSHS_{(M)}$ scores for our population is presented in chapter 3 and shows that both the range of responses and the factor structure matches data recorded elsewhere. The sample size also is larger than that used in many other imaging studies. These two factors, taken together, make 'sampling effects' an unlikely explanation for the failure to find significant support for the continuum hypothesis.
The significance criteria we applied were liberal: the VBM analysis used a voxel-wise threshold of $p < 0.001$ while the individual analyses of the FreeSurfer data used a conventional threshold of $p < 0.05$, but no correction for multiple comparisons. Is it possible that, in spite of this, individual regions show marginally significant correlations with the $LSHS_{(M)}$ scores. The data presented in Table 4.5 speaks a very clear language: only one of the correlations in the sixteen candidate regions, left IFG, shows a negative slope. All other regions show positive slopes. There is, therefore, no question that any significance thresholds are 'slightly' missed.

A secondary look at the data, looking for positive correlations, shows that both structural data analyses show significant *positive* correlations for regions that have previously been linked to hallucinatory experience. The VBM analysis identifies voxels in bilateral STG/MTG and MOG while FreeSurfer shows significant positive correlations in bilateral TTG, left MTG, cuneus and FFG. The regions where effects are found do not overlap, other than in left MTG. A partial explanation may be found in the inherent constraints of the two types of analyses: VBM, since it is a voxel-wise analysis, is more likely than FreeSurfer to show localised effects within large structures, such as STG/MTG, where the structure-average based FreeSurfer analysis may not be sensitive enough. FreeSurfer, however is more likely to show effects in regions that can be clearly structurally delineated, and where effects are more wide-spread.

The Table 4.2 reviewed the brain regions linked with hallucination. It is shows grey matter changes in patients with auditory verbal hallucination compare to the healthy. The Table 4.2 shows reductions in STG, IFG, MFG, Amygdala and Insula in the language processing in patients with auditory verbal hallucination. For VBM in the Table 4.2, identified volume reductions in areas that are broadly linked to language processing and volumetric increases in visual areas (e.g. left occipital grey matter density Nieuwenhuis et al., 2012). These findings

are broadly consistent with the surface based (FreeSurfer) results, Table 4.3, which also identify mostly reduction in volume or thickness of language related brain areas in patients who experience hallucinations compared to controls.

There are, nevertheless, a number of findings that either find no statistically significant differences: Sun et al. (2009), for example, reported that 24% of studies included in their review revealed no substantial difference in the amount of STG and/or its subregions, between hallucinating patients and a control group. Hubl et al. (2010) show opposite results and reported greater grey matter volume in Heschel's gyrus within AVH patients compared to Non-hallucination patients. Also, shin et al., 2005 notices greater grey matter volume in frontal and temporal lobes compare to the Non- hallucination patients.

A recent systematic analysis showed that healthy individual who suffer AVH and Patients with AVH needing treatment, the subjective perceptions involved with AVH were identical. Zhuo et al., 2020 notices significant increase of the gyrification within (left superior temporal gyrus, left temporoparietal junction, superior frontal gyrus., left parietal label), also, significant increased fractal dimensions in the left Wernicke's area, left Broca's areas and left parietal.

Decreases in brain grey matter volume and ventricular enlargement are commonly seen in patients with schizophrenia (Haijma et al., 2013; Shepherd et al., 2012). These differences are seen in first episode psychosis (Chan et al., 2011; Shepherd et al., 2012) but several studies have also reported progressive grey matter volume reductions in time (Andreasen et al., 2011; Chan et al., 2011; Haijma et al., 2013; Shepherd et al., 2012; van Haren et al., 2008). De Moura et al., (2018), using Maximum Uncertainty Linear Discriminant Analysis (MLDA), a machine learning approach, were able to discriminate schizophrenia patients from healthy controls on the basis of volumetric information with a balanced accuracy of over 70.

A potential, partial explanation for being able to distinguish SCZ patients from controls is that antipsychotic drugs, for example haloperidol (Fusar-Poli., 2013) lead to the cortical volume reductions. A direct comparison of (medicated) patients with controls may therefore result in severely confounded data. De Moura et al (2018), were able to show that medication load of SCZ patients was negatively correlated with MLDA score ($r = -.30$, p-value $< .001$), while symptom severity, measured on the PANSS scale, was not correlated with MLDA parameters. The findings of volumetric differences in first episode patients, however, suggest that medication *alone* is unlikely to account for the differences seen between patients and controls.

Social isolation is another possible cause for systematic differences between schizophrenia sufferers and healthy controls that may be reflected in behavioural changes, for example in terms of social interactions. Stahn et al. (2019) [Brain Changes in Response to Long Antarctic Expeditions n engl j med 381;23 nejm.org], compared volumetric brain changes in antartic researchers who for 14 months at the German Neumayer III Station in the Antarctic and found a significant reduction in hippocampal, orbito-frontal and dorsolateral prefrontal cortex volume. Paulik (2012) indicated that the occurrence of AVH might be influenced by interpersonal interactions while Yanos et al. (2010) show that social interactions are an important factor in the recovery continuum of schizophrenia patients. Systematic sampling differences, therefore, may also explain structural differences that are the results of behavioural change caused by hallucinations rather than the cause of hallucinations.

The results are inconsistent with previous studies that have shown reduced lh TTG thicknesses in participants who had auditory hallucinations compared with participants who did not have auditory hallucinations (Mørch-Johnsen et al., 2017; Oertel-Knöchel et al., 2013; van Swam et al., 2012). In addition, my results showed increased both side TTG thicknesses in participants who have high hallucination proneness compared with participants who have low hallucination proneness, which is in line with two other previous studies (Hubl et al., 2010; Shin et al., 2005).

There was a significant positive correlation in voxel based analysis between $LSHS_{(M)}$ scores and auditory areas, in terms of lh (STG/MTG) and rh MTG volume density. Moreover, the $LSHS_{(M)}$ scores correlated in voxel base analysis and shows a positive correlation in visual areas lh & rh (MOG), in terms of the middle occipital gyrus thickness. My results are consistent with a study that found a thicker hippocampal area in participants who had auditory and visual hallucinations, compared to participants who had only auditory hallucinations (Amad et al., 2014). However, (Onitsuka et al., 2007) reported reduction in the grey matter in the visual areas, with hallucinating patients. However, a positive correlation between $LSHS_{(M)}$ scores and MTG thicknesses meant that the MTG was thicker in high hallucination proneness participants than in low hallucination proneness participants. Moreover, previous studies report a positive correlation between hallucination scores and grey matter volume, which is in line with my

study (Modinos et al., 2009). However, Sun et al. (2009) reported that 24% of studies included in his review revealed no substantial difference in the amount of STG and/or its subregions, within both the hallucinating patients' group and the control group.

My results are inconsistent with previous studies that have shown a negative correlation between LSHS scores and volumes (Chen et al., 2015; Gaser et al., 2004; Neckelmann et al., 2006; Palaniyappan et al., 2012). They showed no difference between participants who had high hallucination proneness and those who had low hallucination proneness. I found otherwise for both lh and rh temporal area thickness. This finding suggests that the connectivity between cerebral regions is increased in hallucinating patients. However, there are many studies that have failed to find any relationship between hallucination and STG volume (Allen et al., 2008). Another previous study showed reduced TTG thicknesses in participants who had AVH, compared with participants who had non-auditory hallucinations (Chen et al., 2015). In addition, positive correlation noticed between $LSHS_{(A)}$ scores and left Fusiform which are inconsistent with (Nestor et al., 2007). Fusiform is play role in the faces recognition and volume reduced with schizophrenia patients (Onitsuka et al., 2003). However, a positive significant result reported in this study between $LSHS_{(A)}$ scores and right Precuneus thickness which are in line with (Antonova et al., 2005).

Voxel based analysis confirmed that there is a positive correlation between $LSHS_{(M)}$ scores and some areas in the temporal lobe, such as the TTG and MTG. Moreover, it confirmed that there is a positive correlation between $LSHS_{(M)}$ scores and the lh and rh occipital lobe, namely the OMG. Thus, CAT12 confirmed the FreeSurfer results and the results of the correlations with $LSHS_{(M)}$ scores.

The results in this study are distinct from those of prior MRI structural studies. Such a variation could be related to the characteristics of the samples. For certain patient with hallucination received lithium or antiepileptic medication, the cortical thickness may increase for shorter or longer lifetime cycles (Hibar et al., 2018). Moreover, several studies have shown that volumetric changes in the STG have been caused by psychotic symptoms (Kim et al., 2003) and periods of illness (Liao et al., 2015). Finally, the increase in the grey matter thickness may be a result of the traumagenic neurodevelopmental model, which attempts to integrate what

is known about the neurobiology of psychosis with insights from studies of trauma victims. The trauma lead to change structures such as ventricular enlargement (Read et al., 2005).

4.6 Conclusion

Our data show positive correlations between measures of hallucination scores and measures of brain volume in regions that have previously been shown to show volume reductions in patients that suffer from hallucinations. The continuum model hypotheses (see Figure 4.10, Baumeister et al., 2017), whichever of the three models is considered, do not sit easily with the data presented here.

It is clear that the positive links of volume with $LSHS_{(M)}$ measures we show are the opposite of what would be expected in the quasi-dimensional model. The model proposes that a single variable, for example brain volume in language related areas, predicts the severity of symptoms in the healthy and patient population, and that care-need directly emerges from the severity of the symptoms.

The 'diagnostic discontinuous model' makes a clear distinction between patients and the entire healthy population and their experiences. It states that healthy voice hearers should be indistinguishable as from the rest of the healthy population. Both analyses show significant correlations between hallucination proneness and brain volume, which is inconsistent with this hypothesis.

The fully dimensional model dissociates between variables that predict care need and severity of hallucination symptoms. Systematic differences in variables defining healthy and patients' populations would therefore be indicative of care-need, not hallucination proneness. This would be consistent with functional imaging results, covered in the next chapter (Diederen et al., 2012), which lead to the conclusion that language lateralisation differences are hallmarks of psychosis, but not of hallucination proneness.

The model would, however, predict at least one common variable, linked to hallucination proneness, to be shared across the healthy and patient population. Our data provides no evidence that structural brain measures provide this measure.

All our participants were highly functioning individuals, most of them were university students, yet a significant proportion reported high levels of hallucination proneness and these individuals had higher brain volumes in language areas than those of their colleagues who very rarely or never experienced hallucinations. If reduced brain volume in language related areas is an indicator of the likelihood of psychosis, rather than the cause for hallucinations, then an interesting question is whether relative larger brain volume, and with it perhaps the ability to process complex auditory signals better, may, instead of preventing hallucinations, may enable sufferers from hallucinations to cope with the experience better. This post-hoc explanation would explain that high hallucination proneness is linked to higher brain volumes in the healthy population, yet has been shown to linked with a reduction in brain volume in patients.

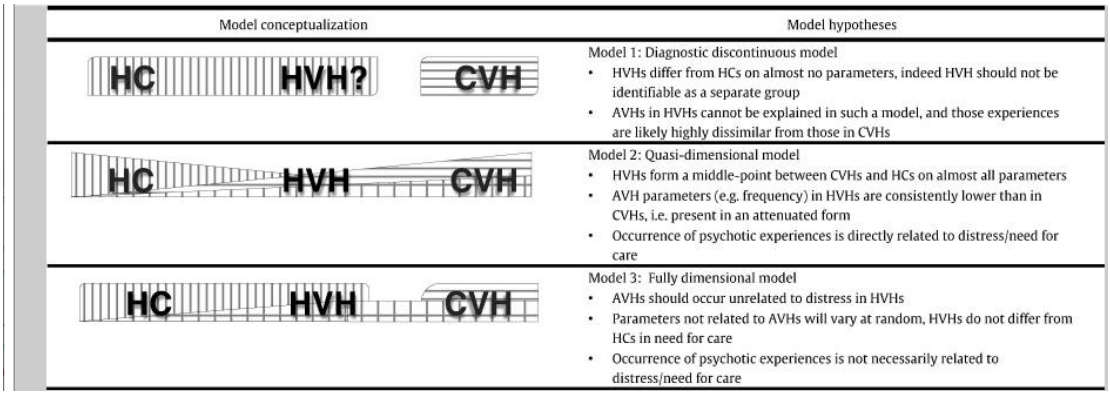

Figure 4.11: The continuum models hypothesis.

Chapter 5

Links between Functional Activation and Hallucination and Hallucination Proneness.

5.1 State vs Trait Effects of Hallucinations and Hallucination Proneness in fMRI

Hallucinations are relatively rare events. Despite this, a variety of experiments have examined neuronal activity while patients experience hallucinations in the absence of external stimulation. In general, this state research indicates increased activation in temporal lobe areas (Dierks et al., 1999; Lennox et al., 2000; Shergill et al., 2004; Suzuki et al., 1993) also in some other language related areas, for example thalamus (Silbersweig et al., 1995), and Broca's area (McGuire et al., 1993,1996). The suggestion that language regions are primarily concerned is consistent with the observation that stimulation is usually left lateralized (Sommer et al., 2003). A meta-analysis found stimulation in the bilateral IFG, bilateral postcentral gyrus and left parietal operculum (Kuehn and Gallinat, 2012) Figure 5.1.

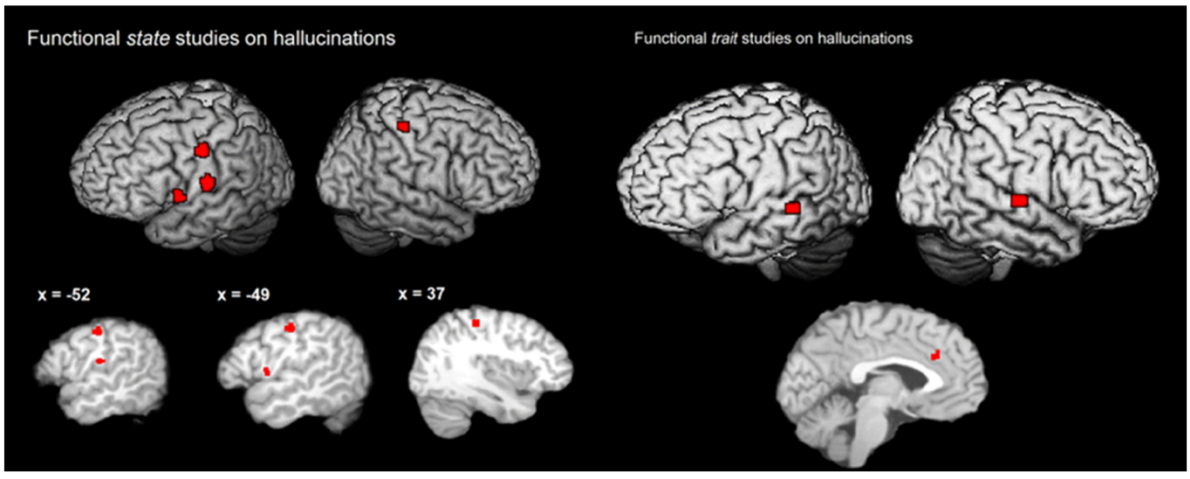

Figure 5.1: State activation likelihood estimation meta-analysis maps for correlates of presence vs absence of auditory verbal hallucination in schizophrenic patients (left) vs Trait activation likelihood estimation meta-analysis maps for between-subject (AVH patients vs non-AVH patients or healthy controls) contrasts (right). Both images from Kuehn and Gallinat (2012).

Functional neuroimaging experiments using externally provided voice stimuli or guidance for generating internal speech in hallucination patients showed decreased neuronal activity relative to control in the same brain regions (Zhang et al., 2008) and compared to non-hallucination patients (McGuire et al., 1996). A meta-analysis of trait studies (Kuhn and Gallinat, 2012) found relative activation reductions in hallucinating participants in the left superior temporal gyrus, left middle temporal gyrus, anterior cingulate cortex and left premotor cortex activity.

The clear separation of brain areas that show increased activation in state studies and other areas that show relative reduction in activation during task performance in trait studies have led to the suggestion that activity seen during AVH states is mainly linked to brain areas that support speech production such as Broca's area or motor cortical areas, while trait studies show that hallucination proneness is related to brain regions associated with the processing of auditory stimuli and speech perception such as auditory cortical and temporal regions.

The studies reported here focus on healthy individuals with a wide range of hallucination proneness scores, see chapter 3. Given the relative rarity of active hallucinations, it is unlikely that hallucinatory states would occur during the functional scans. This means that trait effects, not state effects, can be expected to be seen in the neuroimaging data reported in this chapter.

5.2 Inhibition and Hallucination Proneness

It is well known that functional imaging (fMRI) measures local increases of the BOLD response in functionally relevant brain areas when participants engage in cognitive tasks. While increases in BOLD responses are routinely measured, fMRI studies also often show BOLD reductions in non-stimulated areas of the cortex (e.g. Shmuel et al., 2002). Brain deactivation in task-irrelevant areas is commonly seen in tasks that require attention to single modalities (Deary et al., 2004; Hester et al., 2004; Lawrence et al., 2003). fMRI studies using cross-modal stimuli, for example, showed deactivation in auditory cortices during visual stimulation, and visual deactivation during auditory tasks (Laurienti et al., 2002; Lewis et al., 2000). A plausible explanation for the concomitant deactivation in areas that are not functionally relevant is

cross-modal inhibition (an active suppression of neural activity), to minimize potentially distracting, task-irrelevant neural processes.

Inhibition is also a broad psychological construct which refers executive control that assists behaviour and cognitive skills by focussing attention, learning and memory at specific, task relevant stimuli. The principal role of cognitive inhibition is to suppress irrelevant information and previously activated cognitive contents, and resist interference from competing stimuli (review: Jardi et al., 2016).

Hallucinations are sensory experiences over which the person does not feel they have direct and voluntary control (e.g. Morrison and Baker, 2000). A dominant theory explaining hallucinations, consequently is that intrusive thoughts and the reduced sense of control arises from a breakdown in inhibition (Frith, 1979), and that such deficits might result in the emergence of irrelevant material from long-term memory into awareness (Helmsley, 2005) In support, studies have showed that hallucination frequency in SCZ was associated with difficulties on tasks requiring the suppression of irrelevant information and distracting information (e.g. Waters et al., 2003). Auditory hallucination severity in patients was significantly correlated with error rates in tasks that require participants to voluntarily suppress task-irrelevant mental representations (HSCT task, Burgess and Shallice, 1996), memory traces (ICIM task, Schnider and Ptak, 1999), but also in the suppression of irrelevant sensory information, such as in a Dichotic Listening task (Hugdahl et al., 2013).

Similar deficits have been found in nonclinical groups, such as the group studied here, who score high on a measure of hallucination proneness (Paulik et al., 2007; Badcock et al., 2015). Paulik et al. (2007) reported that hallucination-prone, but otherwise healthy, participants responded with more false alarms on ICIM conditions requiring intentional inhibition than comparison controls, while Badcock et al. (2015) showed that ICIM scores were correlated with hallucination proneness measured on the Cardiff Anomalous Percepts Scale ($r = .38$) but not with LSHS scores ($r = .10$).

Thus, in both clinical and nonclinical groups, there is evidence suggesting that hallucination proneness is related to intentional inhibition. This is consistent with the continuum theory, it is therefore possible to make specific predictions that hallucination proneness scores in a

healthy group should be correlated with functional measures of inhibition in tasks that require the suppression of irrelevant sensory, in particularly auditory, information.

5.2.1 Testing whether impaired inhibition is linked to increased hallucination proneness

Hugdahl and colleagues (2008,2009,2012) make the case that hallucinating patients have problems in processing external speech sounds when experiencing ongoing hallucinations but also when instructed to use attention to better focus on the external stimulus. Hugdahl et al. (2009) argue that auditory hallucinations are caused by neuronal abnormality originating in the left temporal lobe speech areas and/or neuronal grey matter pathology. The team cites evidence that the phenomenon is paralleled in grey matter reduction in temporal lobe areas, as reviewed in the previous chapter. They argue that their view is also in agreement with other studies on auditory verbal hallucinations, for e.g., 'mis-representations of inner experiences' (Heinks-Maldonado et al., 2007), 'mis-attribution of speech' (Allen et al., 2007), 'mis-attributed cognitions and inner speech' (Kinderman, 2007) or that auditory hallucinations may be 'competitions between auditory stimuli and competition for physiological resources in the temporal cortex' (Hubl et al., 2007).

The hypothesis that hallucinations are linked to an imbalance of excitation or inhibition is supported by trait studies, which mainly explored verbal self-monitoring, verbal imagery, and source memory (review Allen et al., 2012). Experimental data shows that schizophrenia patients who experience AVH exhibit decreased activation within temporal, cingulate, premotor, and subcortical regions that support typical tasks carried out in the scanner (Kuehn and Gallinat, 2012).

A different explanation for hallucination, which nevertheless would result in similar observed fMRI data has been proposed by Horga et al. (2014). They used fMRI modelling to compute a 'prediction error', this is the difference between observed and predicted signal in response to speech stimuli in relevant areas. The authors argue that this prediction error correlates strongly with the observed fMRI activation during silence, weakened responses to unexpected speech, and reduced volumes in "auditory cortex" although they really show

MTG volume decreases in hallucinators, consistent with other studies that compared hallucinating patients with healthy controls. Their central argument is that patients with more severe AVH exhibit more severe prediction errors and greater activity in auditory regions during silence and that deficient predictive coding, rather than inhibition as proposed by other authors, is the cause for resting hyperactivity in sensory cortex which is the cause for hallucinations.

Both explanations propose a neurocognitive model for auditory hallucinations, which emphasizes perceptual mis-representations caused by neuronal abnormality in the temporal lobe areas, Figure 5.2, from Hugdahl 2009.

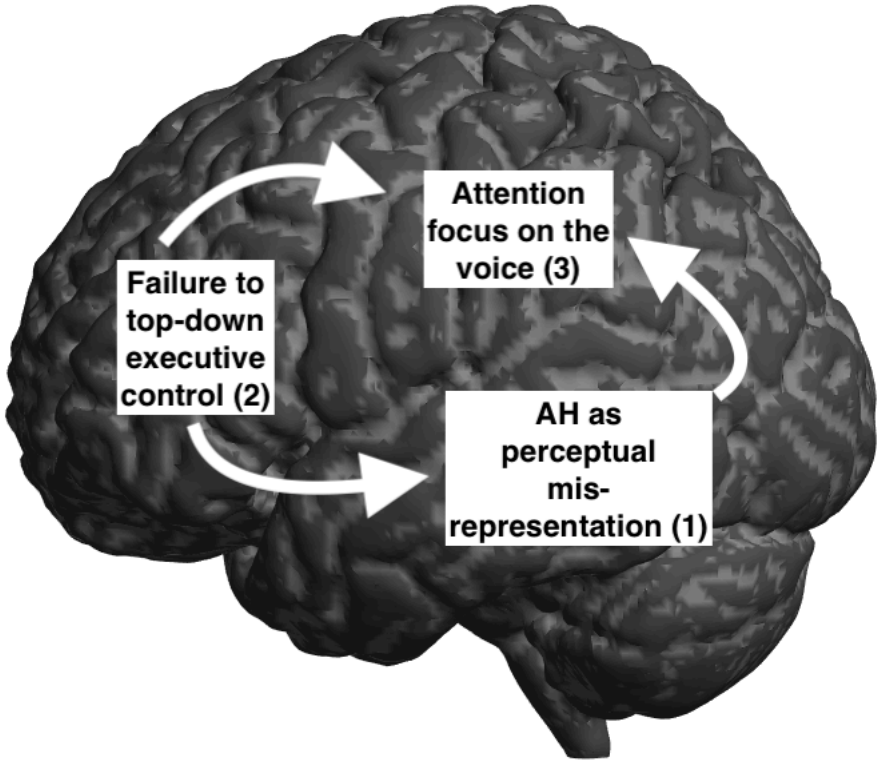

Figure 5.2: Hugdahl's (2009) model for auditory hallucinations (AH) as perceptual mis-representations, parietal lobe attention enhancement and failure of prefrontal executive suppression control. The model emphasizes the involvement of the middle and superior temporal gyri (1) for the generation of AH, prefrontal cortex (2) for top–down executive control, and parietal cortex (3) for attention focus.

Both explanations for hallucinatory experiences lead to the same testable hypotheses in the context of fMRI experiments: If patients show consistently lower signal-specific activation in task-relevant regions and simultaneous less suppression of activity in non-task-relevant areas, then activity in these regions should be, at least partially, predicted by hallucination proneness measures in healthy controls.

The claims that hallucination proneness is linked to relatively less modulation of activity in task relevant areas is not universally supported. Lewis-Hanna et al. (2011), in a comparison of 12 sleep-related hallucination prone participants with 12 controls, for example found greater speech-evoked activation in the left angular gyrus for hallucinators than for controls and more modulation of the anterior cingulate during selective auditory attention. They explain their findings with an enhanced attentional bias and increased sensitivity in auditory regions in hallucinators. The relatively small groups size and specific participant group (sleep-related hallucinations) means that the results may not transfer easily to other groups or generalise to larger cohorts.

5.3 Language lateralisation

Reduced left functional dominance in schizophrenia has been hypothesized for many years based on anatomical studies, investigations of handedness and dichotic listening (for a review, see Sommer et al., 2001b). This reduced lateralization may reflect either a failure to inhibit the non-dominant language areas or a more bilateral cortical representation of language function in schizophrenia.

Neuroimaging studies using verbal fluency tasks in schizophrenia patients have produced conflicting findings: Some authors have reported reduced (left lateralised) inferio-frontal activity during the performance of verbal fluency tasks (Curtis et al., 1998, Yurgelun-Todd et al., 1996, Artiges et al., 2000, Kim et al., 2000, Boksman et al., 2005, Kircher et al., 2002, Dollfus et al., 2005) while others have found normal activity of the left but increased activity of the right inferior-frontal cortex, which also leads to decreased language lateralization (Sommer et al., 2001a, Sommer et al., 2003). Language lateralization of the inferior frontal cortex is similarly reduced in medicated (Weiss et al., 2002) and unmedicated (Weiss et al., 2006) patients relative to healthy controls. Weiss (2006) also reports that the difference in lateralisation index was mostly attributable to activation patterns in Broca's area

and its right hemisphere homologue and that these differences are related to the severity of hallucinations.

Brain structures that are functionally associated with language or auditory processing. Language areas consisted of the inferior frontal gyrus, insula, middle temporal gyrus, superior temporal gyrus and angular.

It is an open question whether these findings in patient populations transfer to healthy voice hearers. Diederen et al. (2010) measured lateralisation patterns non-psychotic controls with and without AVH and patients with AVH and, while showing reduced lateralisation in psychotic patients, were unable to demonstrate lateralisation differences between healthy controls and participants who experienced AVH. The mean lateralization index was 0.35 (SD 0.29) for the healthy control subjects, 0.27 (SD 0.33) for the non-psychotic subjects with AVH and 0.02 (SD 0.38) for the patients with psychosis. The authors conclude that language lateralisation differences are hallmarks of psychosis, but **not** of hallucination proneness. A potential criticism of the Diederen study is that the 'healthy AVH' participants were selected via opportunity sampling (via a website) and 'high scores' in only two of the LSHS questions, items 8 'In the past, I have had the experience of a person's voice and then found that no-one was there' and item 12 'I have been troubled by hearing voices in my head', were used to select participants. A more differentiated approach, such as using the full $LSHS_{(M)}$ score or the 'auditory subset' as a regressor rather than as a categorical 'group selector' might uncover systematic effects of the hallucination proneness trait.

Hypotheses:

If CVH show significantly reduced lateralisation in IFG regions during CWG tasks, and if these reductions are linked to hallucination severity, then continuum theories would predict that lateralisation indices in healthy participants are negatively correlated with $LSHS_{(M)}$ scores in these regions.

5.3.1 Measuring Language fMRI and Lateralisation

5.3.1.1 Justification for our language tasks

Cued word generation

Verbal fluency tasks have been widely used to evaluate language and executive control processes in the human brain. The most commonly used task to measure language lateralisation is a 'cued word generation' (CWG): participants are presented with a single letter and are asked to, overtly or covertly, generate as many words as possible that start with this letter. Block designs are well established: CWG task blocks, around 30 seconds long, typically alternate with matched rest blocks.

The major advantage of this task is that it is very widely used, so that baseline data ubiquitous. There are, however, significant disadvantages associated with covert or overt CWG tasks in the context of fMRI experiments. FMRI studies of verbal fluency typically use either covert (silent) word generation, which provides no behavioural measure, or cued generation of *single* words in order to avoid speech-related motion artifacts. Asking participants to only report a single word may not be sufficiently challenging to elicit reliable BOLD responses. Additionally, as pointed out by Sommer et al. (2001a), task performance can be a significant confounding factor in fMRI experiments that compare patients with healthy controls, because poorly performing patients may not generate enough words in an unpaced verbal fluency task, potentially resulting in reduced language centre activation and a consequent bias towards reduced language lateralisation.

A number of alternative language tasks that provide a more differentiated activation patterns, for example listening vs reading, more reliable lateralisation data and the ability to collect behavioural data to assess performance and demonstrate engagement with the task have been proposed. Arora et al. (2009) systematically examined the efficacy of three tasks, reading sentence comprehension, auditory sentence comprehension, and a verbal fluency task. Lateralisation indices were compared validated against a ground truth provided by Wada testing. For the lateralized patients categorized by Wada, fMRI laterality indices (LIs) were concordant with the Wada procedure results in 83.87% patients for the reading task, 83.33%

patients for the auditory task, 76.92% patients for the verbal fluency task, and in 91.3% patients for the conjunction analysis.

Sentence comprehension, whether the sentences are presented in writing or spoken, produces reliable lateralisation data, and therefore enables testing theories that link language lateralisation with hallucination proneness.

Asking participants to perform the task twice, once listening to sentences, once reading text presented on a screen, means that brain areas involved in general language processing can be separated from low-level auditory and visual processing.

Hypotheses:

1- Reduced excitation in task-relevant areas. If hallucination proneness is linked to a reduction in task relevant areas during language tasks, then we expect negative correlations between $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ scores with BOLD response in language relevant areas: left superior temporal gyrus, left middle temporal gyrus, anterior cingulate cortex, inferior frontal gyrus).
Similarly, $LSHS_{(V)}$ scores will correlate negatively with activation in task relevant visual areas in the 'faces' and audio/visual task: (Fusiform, Amygdala, occipital lobe and middle frontal gyrus) (Boubela et al., 2015).

2- Reduced inhibition in non-task-relevant areas. The same analysis that is used to test whether $LSHS_{(M)}$ scores are corelated with activation in task-relevant areas can be used to test whether $LSHS_{(M)}$ scores in areas that are not task relevant are correlated with BOLD response. Since the visual and auditory tasks are complementary, ROIs defined as areas where significant responses are seen in one, but not the other set of tasks can be used as areas where inhibition is expected.

3- Reduced lateralisation – reduced lateralisation for language tasks has been proposed as a correlate of hallucinatory experiences in patients. If a continuum between healthy voice hearers and patients exists a negative correlation of $LSHS_{(M)}$ scores with the Lateralisation Index, perhaps in specific areas, should be observed.

5.3.1.2 Justification of our visual tasks

Visual perceptual abnormalities (VPA), just like auditory hallucinations, are common experiences in first-episode psychosis and chronic schizophrenia/schizoaffective disorder (SZ/SA) patients. VPAs and illness duration, symptom severity, current functioning, premorbid functioning, diagnosis, and age of onset.

Keane et al. (2018) describe abnormal perception of bodies, faces, and object motion in psychosis and argue that the experiences may be explained by abnormal brain activation patterns in associated brain structures, namely medial temporal cortex (motion), posterior superior temporal sulcus (bodies), and fusiform gyrus (FFA, faces) (Bauser et al., 2012; Chen, 2011; O'Donnell et al., 1996; Kim et al., 2011; Marwick & Hall, 2008).

The two temporal cortical areas, especially the pSTS, are also closely involved in language processing and there is an argument that these areas, together with inferior frontal areas are involved in action perception, which encompasses both speech and body actions (Hein and Knight, 2008). With this background it is therefore perhaps not surprising that auditory and visual hallucinations commonly co-occur. The FFA, on the other hand provides a distinct neural substrate that is specifically linked to the processing of 'faces' and where abnormalities may lead to specific hallucinatory experiences.

5.3.1.3 Face specific processing in the Fusiform Face Area

Face recognition, just like language processing, is critical for human social interactions. Studies of patients showing individual face recognition impairment after brain damage (prosopagnosia, e.g. Della Sala and Young, 2003) show that face processing is supported by a distinct brain area in the human ventral occipito-temporal cortex (VOTC), from the occipital pole to the temporal pole, with a right hemispheric advantage (Busigny, 2010; Barton, 2008). Functional imaging experiments have identified face-selective responses in the lateral section of the right posterior/middle fusiform gyrus (FG), often referred to as the Fusiform Face Area (FFA) (review Kanwisher, 2017). Electrical stimulation of this area has been shown to be able to elicit face identity hallucinations (palinopsia).

Keane et al., (2018) identify differences in the occurrence of (other) face/body perception [$t(30) = 2.96$; $p = 0.036$], and changes in own face perception [$t(30) = 2.62$; $p = 0.047$] as two visual perceptual abnormalities that distinguish schizophrenia/schizoaffective (SZ/SA) patients from patients with other psychotic disorders. Other common visual illusions are

object pseudomovement [t(30.0) = 2.68; p = 0.047], and double/reversed vision [t(30.0) = 3.78; p = 0.01], which are more likely to be linked to abnormalities in earlier visual processing. A 'face recognition task' therefore provides data on a specific hallucinatory experience and for a specific brain area (the FFA). The task also draws on a wide range of low-level visual processing so that systematic differences in task-related brain activation, analogous to the differences proposed for the language tasks, can be identified.

Hypothesis:

we expect task related activation in the FFA, and possibly in early visual processing areas, is modulated by the $LSHS_{(M)}$ scores.
If hallucination proneness modulates the ability to inhibit task irrelevant areas, then one would expect activity in language specific areas (and identified using the two language tasks) to be depressed less in participants that show high $LSHS_{(M)}$ scores.

5.3.1.4 AV detection task

As reviewed above, it has been argued that hallucinations derive from a failure of inhibition (e.g. Frith., 1979). Behavioural data, for example data on dichotic listening supports this view. The final task chosen was designed to test this explicitly by asking participants to respond (selectively) to a visual target (grating flashing) while ignoring an auditory distractor (beep sound). This signal was presented asynchronously with the visual stimulus, so that in some cases the two signals are coincident, but in the majority of cases the auditory signal either precedes or follows the target signal.
To perform the task, participants have to ignore the non-information-bearing auditory beep. Pervious work has shown that the reaction times of participants with high LSHS scores are more influenced by preceding auditory signals than for low scorers. The finding may reflect a deficit in selective attention, specifically the ability to ignore the task-irrelevant auditory signal.
The visual attention tasks therefore provide an opportunity to test claims that selective attention, either positive attention to the visual signal, or the ability to suppress task-irrelevant auditory activity is linked to the trait of hallucination proneness.

Hypotheses:

If selective attention to task-relevant signals is impaired in participants with high hallucination proneness, then $LSHS_{(M)}$ scores and activation in visual areas should be negatively correlated, while correlations in (task-irrelevant) auditory areas should be positive.

5.4 Methodology

5.4.1 Participants

This study was conducted in the Liverpool Magnetic Resonance Imaging Centre (LiMRIC) at the University of Liverpool. The study was approved by the university ethical committee. The ethical approval reference number is IPHS-1516-LB-128 on 17/12/2015. This study was done in conformity with the committee policies. An online Launay-Slade Scale Modified questionnaire $LSHS_{(M)}$ was created and distributed via university email Figure 5.3. Seventy-five participants completed the $LSHS_{(M)}$ questionnaire on Qualtrics online. 75 participants agreed to do MRI scan. 6 participants out of 75 excluded because they had metal implants. 69 participants underwent in the MRI scan. MRI scanning abnormalities were identified in one participant and these were reported to the participants GP by the Walton hospital neuroradiologist. Moreover, two participants excluded because there are no data available from the task to analysis the images. The final number was 66 participants for voice and text, and faces sequences; 27 males and 39 females with average age 29.1 years (SD=11.956; range, 18-66). The final number of participants for the audio-visual detection experiment was 55 participants because task added later to the study; 17 males and 38 females with age average 26.93 years (SD=9.783); range 18-66).

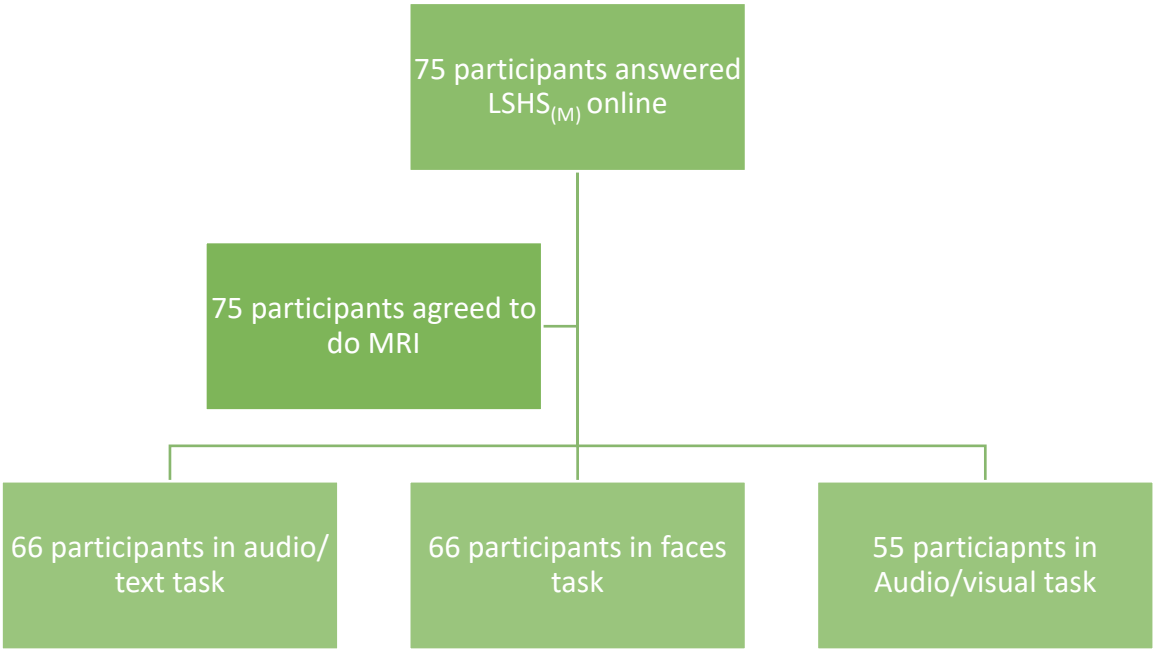

Figure 5.3: Number of participants in this study.

5.4.2 fMRI (Voice & Text) Task

The audio and text fMRI sequence consisted of two parts, the MRI sequence and the task which was designed by PsychoPy and run from the laptop. Both of them were run at the same time. The sequence parameters were TR 3000 ms, TE 30.0 ms, Flip angle 90 degrees slices 48, slice thickness 2.7 mm, voxel size 3.0 x 3.0 x 2.7 mm, FoV 192 mm. The task was designed employing the PsychoPy 2 V3.0.4 software. It was a block design and consisted of 20 blocks; each block was 16 seconds. The total time for this task was approximately 10 minutes. There were three conditions in this task; rest, audio and text. The task always started with rest and was followed by either an audio or text block, then followed by rest again and either an audio or text etc until the task was completed. The audio and text task were designed to run randomly. For example, it was possible that three text blocks followed to the rest and then one block of audio. In the block of audio and text, the participants either saw the sentence as text and were asked to respond if the statement was correct by pressing the C button or by pressing the B button if the statement was false. During the audio block, the participants were presented with a voice and were asked to respond if what they heard was correct by pressing the button C or pressing the button B if the statement was false.

5.4.3 fMRI Faces Task

The sequence parameters were TR 3000 ms, TE 30.0 ms, Flip angle 90 deg slices 48, slice thickness 2.7 mm, voxel size 3.0 x 3.0 x 2.7 mm, FoV 192 mm. The faces task was designed using the PsychoPy 2 V3.0.4 programme. There were only two conditions for this task, rest and active. The total number of the blocks was 20. In the rest, the screen was blank and participants were not requested to respond. During the active block, the participants were presented with faces. Figure 5.2. In all instances the order for the task block was sequential and participants were presented with the rest block (16 seconds) then the faces block (16 seconds) until task end. The faces show up sequentially and if it is duplicate participants will press the button. In Figure 5.4 faces (B) is repeated again in face (D), so participants need to response by pressing the button.

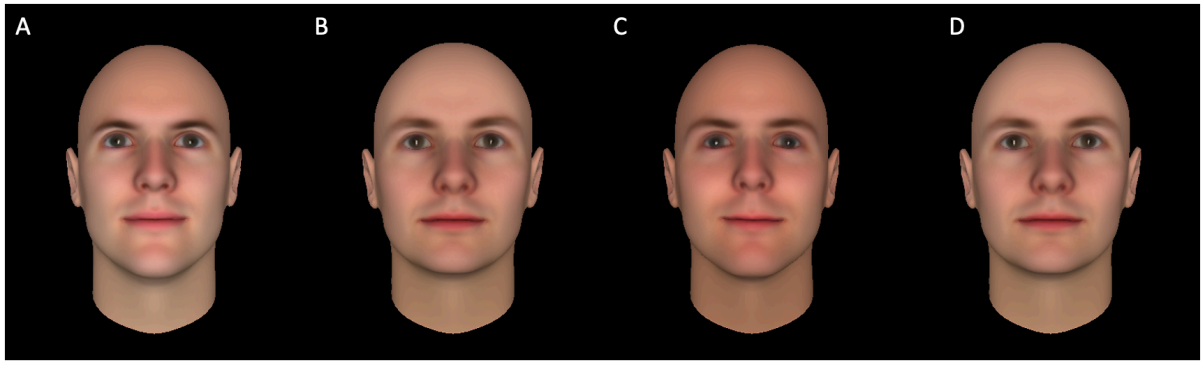

Figure 5.4: Faces used in faces task. Face in (D) is duplicated of faces (B).

5.4.4 fMRI Audio/Visual (A/V) Task

This task was designed as a block design using MATLAB. The task started with a 16 second rest block, followed by a 16 second task block. The sequence parameters used were TR 1500 ms, TE 30.0 ms, Flip angle 90 deg slices 48, slice thickness 2.7 mm, voxel size 3.0 x 3.0 x 2.7 mm, FoV 192 mm, multi slice. In this task, the participants were presented with a white grating on the screen, as illustrated in Figure 5.5 (A). Either less than a second prior, simultaneously or after this grating flashed on the screen, the participant was presented with a beep, Figure 5.5 (B). Participants were instructed to ignore the beep and only respond by pressing the button when they observed the grating flashing.

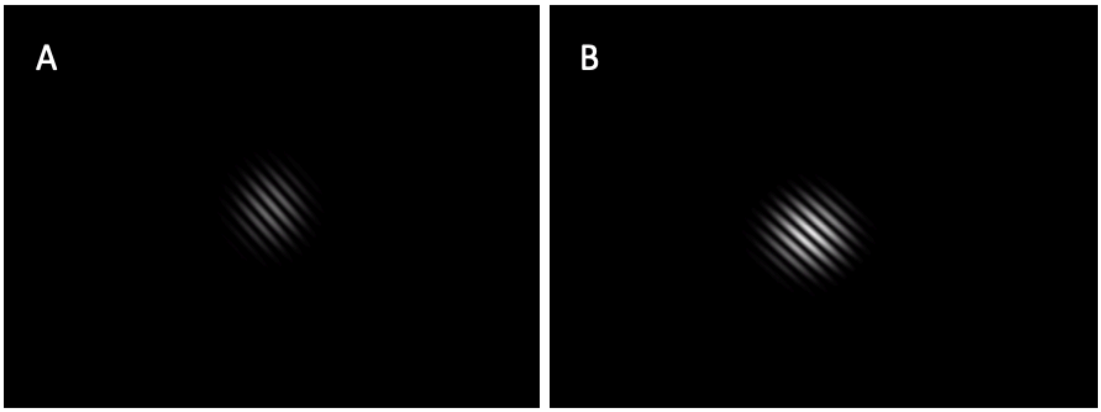

Figure 5.5: A grating before flashing. B grating during flashing.

5.4.5 Auditory Stimulus Presentation

MR Confon Starter f MKII Version R05 July 2017 was used to deliver the sound to the participants from the console room. It consisted of a control unit, fiber optic, headphone and microphone. From the control unit, fiber optic wires entered the MRI room ending with headphones. The participants were asked to put on the headphones and through these, the sound was delivered. The headphones were designed to suppress the noise from the scanner to a specific level. Another output cable from the control unit connected to the computer was used to run the sounds file or stimuli.

5.4.6 Visual Stimulus Presentation

NordicNeuroLab is a visual system that consists of an Inroom Viewing Device, ResponseGrip, SyncBox and nordicAktiva. NordicAktiva is the tailored paradigm library in the console room used to build, modify or run pre-defined the experiment. Inside the scanner room, the Inroom Viewing Device 40 4K UHD showed high definition and superior image quality. ResponseGrip was the patient response device made from fiber optic and connected to the SyncBox. SyncBox is a small box connected to the ResponseGrip, nordicAktiva and MRI scanner. It ran stimuli and image acquisition at the same time. Moreover, it allowed synchronization signals to come from a subject through ResponseGrip and provide accurate logging of time stamps via LED indicators and optional sound signalling.

5.4.7 fMRI Image Preprocessing

Pre-processing on the fMRI images was performed employing SPM12 (Statistical Parametric Mapping). Preprocessing was performed in two stages. The first stage includes six steps. The first step, referred to as reslice timing, repositions all the images including the first image to keep it all in the original space. The second step realigned the time-series employing the first image as a reference. The third step, unwarp, removes artefacts from the images. The fourth step, referred to as image segment, corrects bias and normalises spatially. The fifth step, coregister, merges the anatomical images and the mean of the fMRI images. Next, the normalisation step was applied to align both anatomical and fMRI images in the standard space. Finally, the smooth step averages the data across a wider range of voxels. The second stage of the fMRI analysis included using the model specification batch in SPM12, which is a statistical analysis of fMRI data. It operates a mass-univariate method based on General Linear Models (GLM) and involves three steps: specification, estimation and interrogation of results.

5.4.8 Regions associated with auditory and visual hallucination

Areas related to the auditory and visual hallucinations extracted. WFU_PickAtlas (https://www.nitrc.org/projects/wfu_pickatlas/) provides a method for generating masks in the regions of interest (ROI) based on the Talairach Daemon database. The activation in the ROI related to the auditory and visual hallucination were extracted (cingulate, Fusiform, inferior frontal gyrus (IFG), Insula, inferior temporal gyrus (ITG), middle frontal gyrus (MFG), middle temporal gyrus (MTG), superior frontal gyrus (SFG), superior temporal gyrus (STG), transverse temporal gyrus (TTG), superior occipital (SO) and middle occipital (MO).

The influence of the hemisphere in fMRI seen through a calculation known as the laterality index (LI) (Seghier, 2008). REX is a MATLAB based toolkit and used to extract the data from the region of interest in the fMRI data (https://www.nitrc.org/projects/rex/). Language related stimulated clusters were collected independently within the mentioned anatomical landmarks ($P < 0.05$), using GLM as a positive predictor for the voice condition and the rest condition as a negative predictor. In addition, using GLM as a positive predictor for the text condition and the rest condition as a negative predictor. For each subject the number of

activation voxels in each of the given ROI on the left and right hemispheres was counted separately. Those number were used to measure a language-related lateralization index (LI) for each area (i.e., LI=L-R/L+R, with L=number of voxels to the left and R= number of voxels to the right). The further positive the number, the more left side the activation, while the further negative the number, the more to the right side the activation (Bleich-Cohen et al., 2009). The laterality index (LI) for each region associated with hallucination calculated and correlate with $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$. GraphPad prism version 8.4.3 used in correlation. Data did not pass normality test. Non-parametric correlation performed in all correlation.

5.5 Data analysis

5.5.1 Relevant tasks

Brain activation in regions relevant to the tasks (voice and text, faces and audio/visual) correlated to the hallucination severity ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$).

5.5.2 Inhibition

Brain activation in regions irrelevant to the tasks in faces and audio/visual tasks (frontal and temporal) corelated to the hallucination severity ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$).

5.5.3 Lateralization Index

The following anatomical masks were used in the language conditions (voice and text comprehension tasks): IFG, MFG, TTG, STG, MTG, and ITG. For each subject the number of active voxels in each of the given ROI was counted separately at $p< 0.05$. The counts were used to calculate a language index (LI) for each area (i.e., LI=L−R/L+R, with L=number of voxels on the left and R = number of voxels on the right) (Bleich-Cohen et al., 2009). The result of the LI was correlated with ($LSHS_{(M)}$, $LSHS_{(A)}$, $LSHS_{(V)}$). Positive numbers indicate, left activation lateralisation, while a negative number indicates lateralization to the right.

5.6 Results

Figure 5.6 shows the activation of the four conditions and included tables of the regions associated with auditory and visual hallucination.

Regions	Voice	Text	Faces	AV	ANAT links
SFG	Yes	Yes	Yes	Yes	No
MFG	Yes	Yes	Yes	Yes	Yes
IFG	Yes	Yes	Yes	Yes	Yes
TTG	Yes	Yes	No	No	Yes
STG	Yes	Yes	No	Yes	Yes
MTG	Yes	Yes	No	Yes	Yes
ITG	Yes	Yes	No	No	No
Insula	Yes	Yes	Yes	Yes	Yes
Fusiform	No	Yes	Yes	No	Yes
Lingual	Yes	No	Yes	No	No
Cingulate	Yes	No	Yes	No	No
Cuneus	Yes	No	Yes	Yes	No
MOG	No	Yes	Yes	Yes	Yes
IOL	No	Yes	Yes	No	No
Declive	No	No	No	yes	No
IPL	Yes	No	No	Yes	No
SMG	No	No	Yes	No	No
Precuneus.	No	No	No	No	Yes

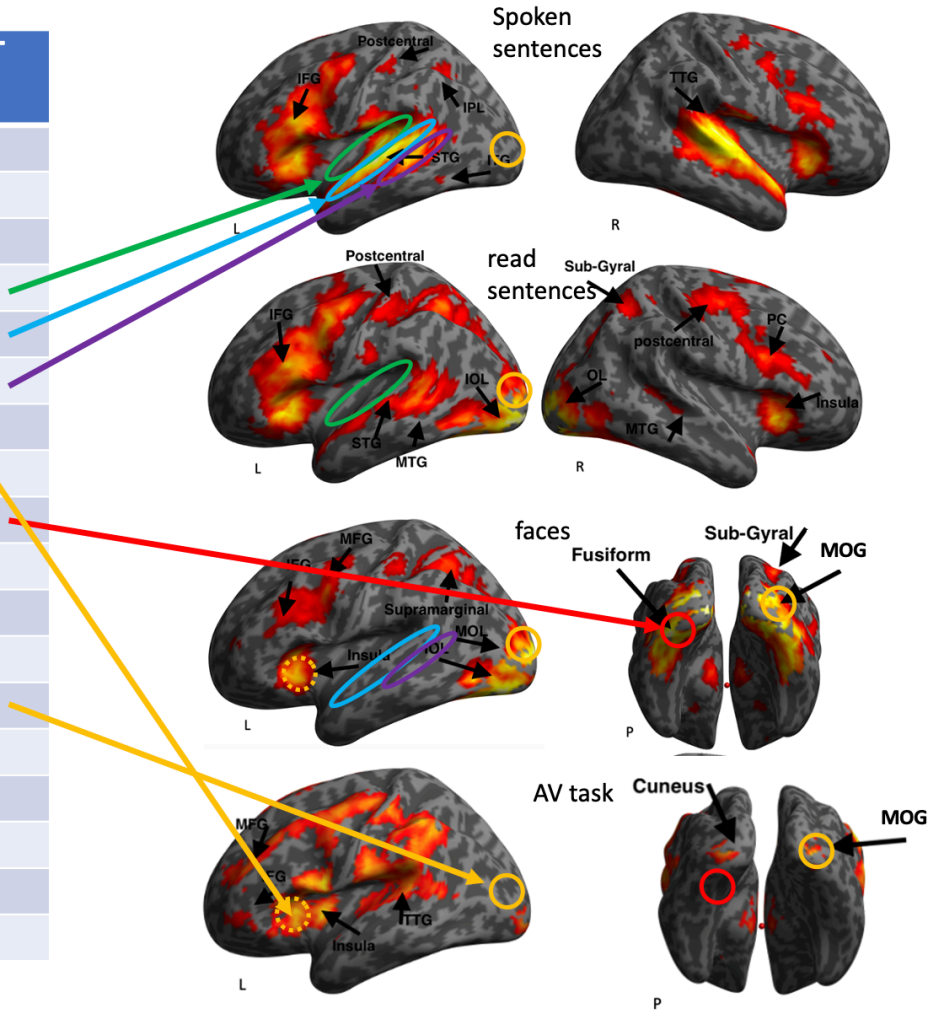

Figure 5.6: Shows the activation of the areas in the four conditions.

5.6.1 Relevant tasks

5.6.1.1 Voice comprehension condition

FMRI action increases during the voice condition were seen in bilateral TTG, STG, MTG, ITG, IFG and MFG at (p_{FWE}<0.05). Figure 5.7 shows an example correlation between the estimated beta values in the left and right TTG with $LSHS_{(M)}$. None of the correlations between activation and LSHS scores were significant. Figure 5.7 shows a positive correlation TTG bilateral with $LSHS_{(M)}$. All other regions showed positive correlations relating language activation with hallucination proneness scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$). Full results are shown in appendix C1-1, C1-2 and C1-3. However, no correlation was significant.

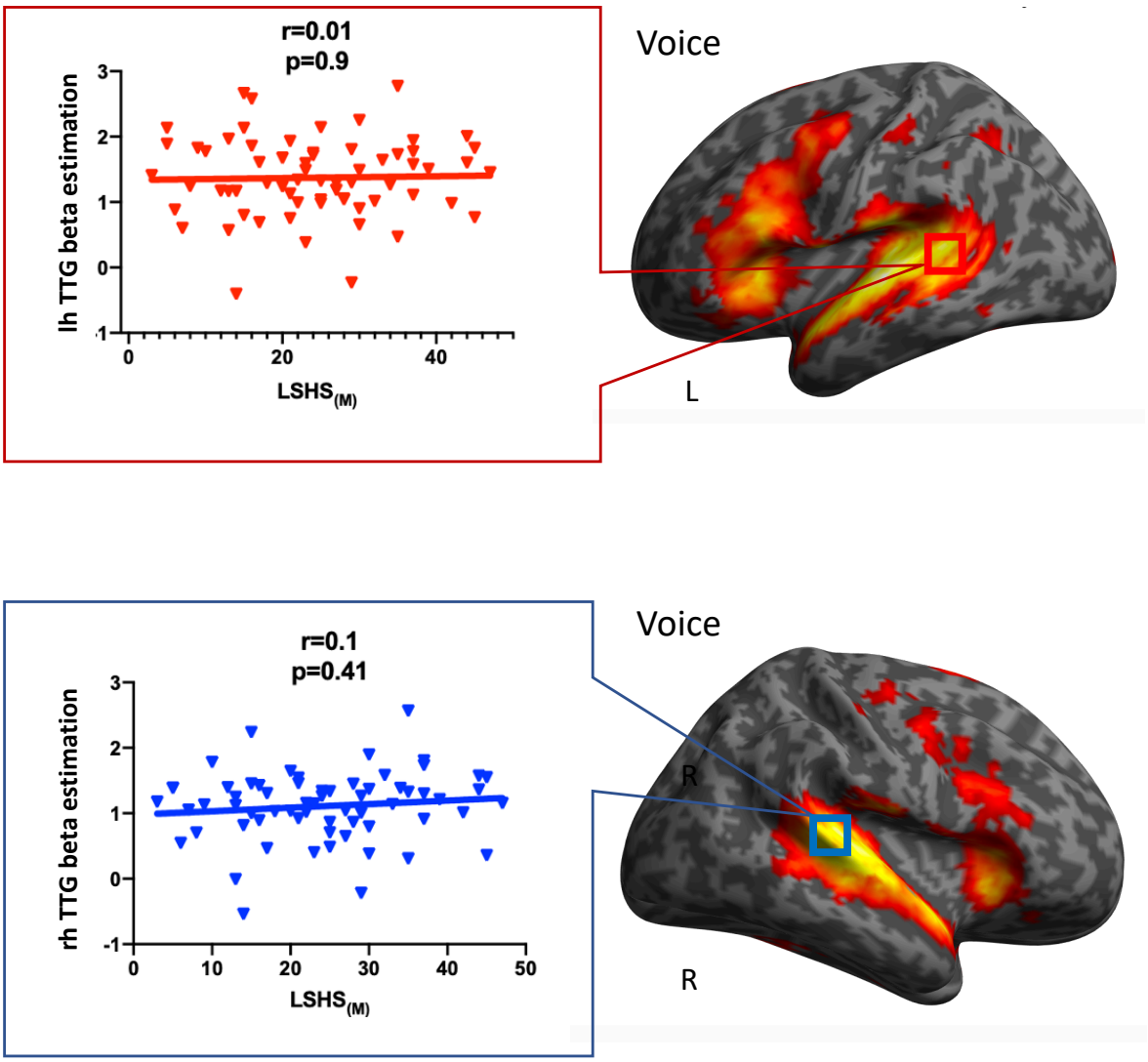

Figure 5.7: Shows a positive correlation between $LSHS_{(M)}$ scores and bilateral TTG beta estimation in the voice condition.

5.6.1.2 Text comprehension condition

Similar the 'voice' condition, significant activation clusters in the fMRI were seen in bilateral in TTG, STG, MTG, ITG, IFG, MFG and MOG at (p_{FWE}<0.05), Figure 5.8. None of the correlations between activation and $LSHS_{(M)}$ scores were significant. An example, very slightly positive, between the bilateral transverse temporal gyrus (TTG) and $LSHS_{(M)}$ is shown. A full set of results is shown in appendix C2-1, C2-2 and C2-3.

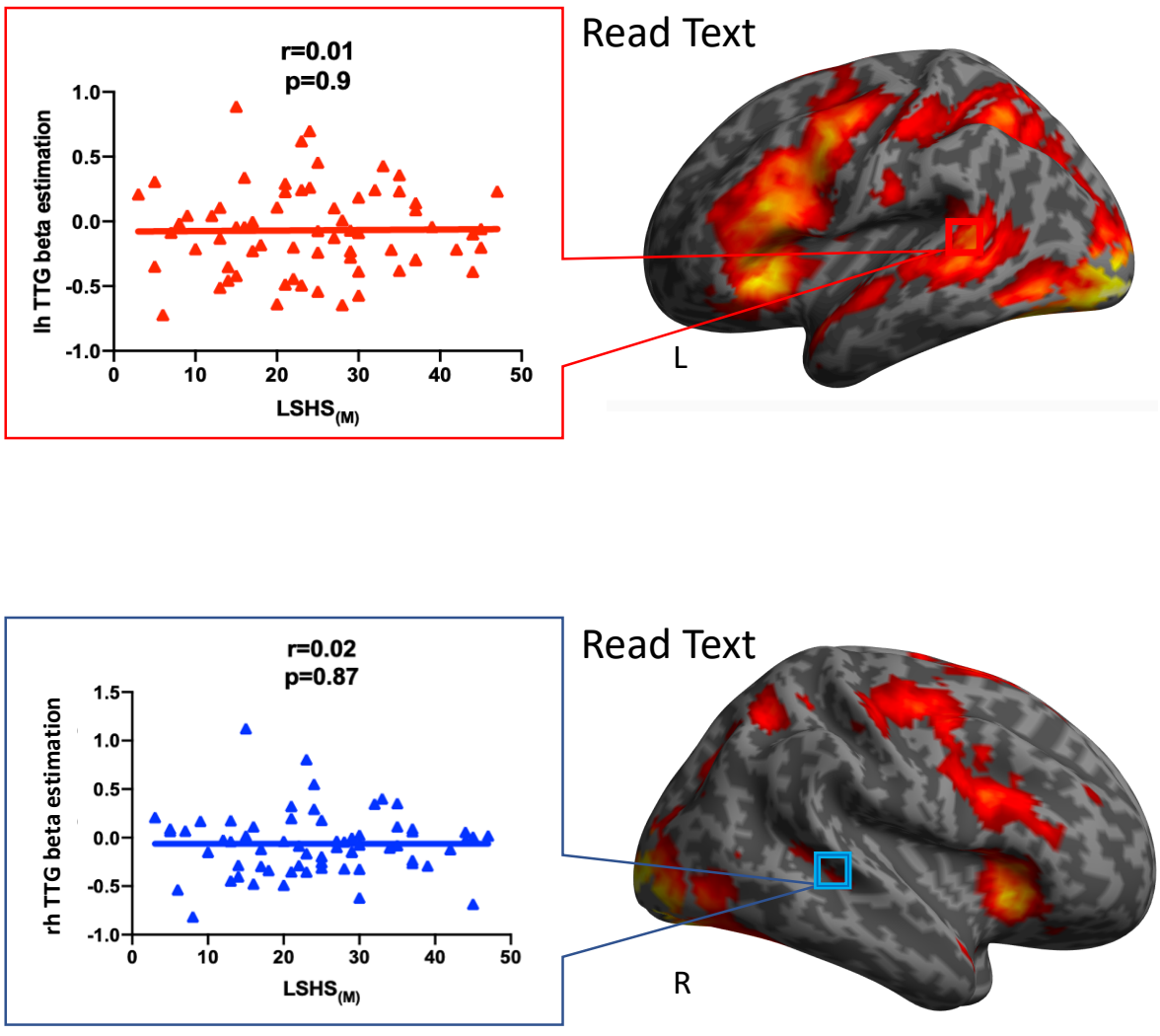

Figure 5.8: Shows a positive correlation between $LSHS_{(M)}$ scores and bilateral TTG beta estimation in the text condition. Left transverse temporal gyrus (red). Right transverse temporal gyrus (blue).

5.6.1.3 Faces task

The face perception task caused significant activation clusters in bilateral in Fusiform, MOG and SOG at (p_{FWE}<0.05). As for the other conditions, no significant correlations between activation and $LSHS_{(M)}$ scores were found in task-relevant areas (Fusiform, SOG and MOG) and, as before, full results are shown in appendices C3-1, C3-2 and C3-3. Figure 5.9 shows a typical, slightly positive, correlation between $LSHS_{(M)}$ scores and brain activation in faces task in (left Fusiform & right MOG).

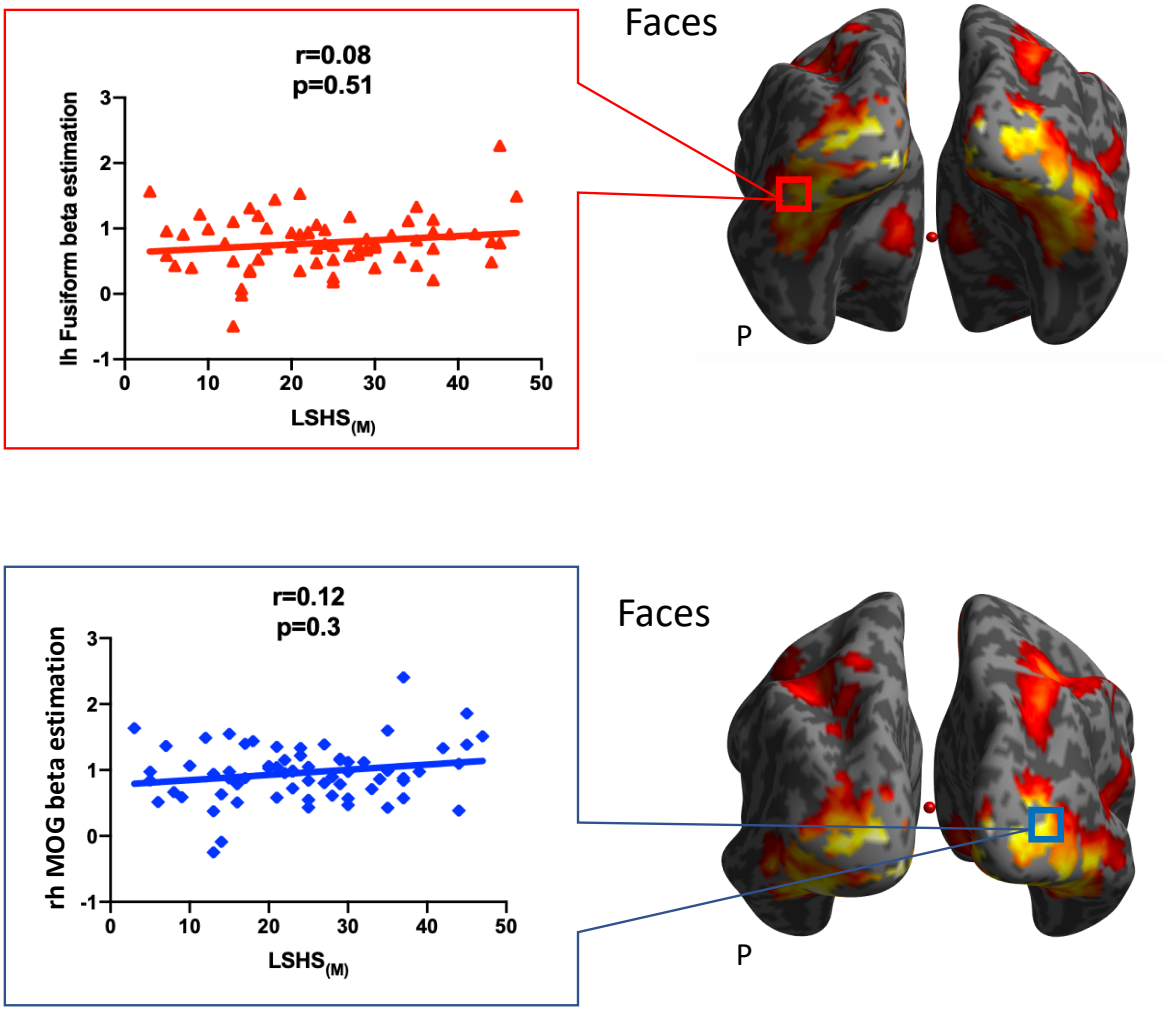

Figure 5.9: Shows a positive correlation between $LSHS_{(M)}$ scores and left Fusiform activation (red) in the faces task. In addition, a positive correlation between the right middle occipital gyrus (blue) activation and $LSHS_{(M)}$ scores in faces task.

5.6.1.4 Audio/Visual task

The audio-visual task caused task-relevant activation on the two task relevant areas, MOG and SOG, was not significantly correlated with $LSHS_{(M)}$, $LSHS_{(A)}$ or $LSHS_{(V)}$ scores (appendices C4-1, C4-2 and C4-3. An example correlation plot between activity in a significantly activated cluster and $LSHS_{(M)}$ us shown in Figure. 5.10.

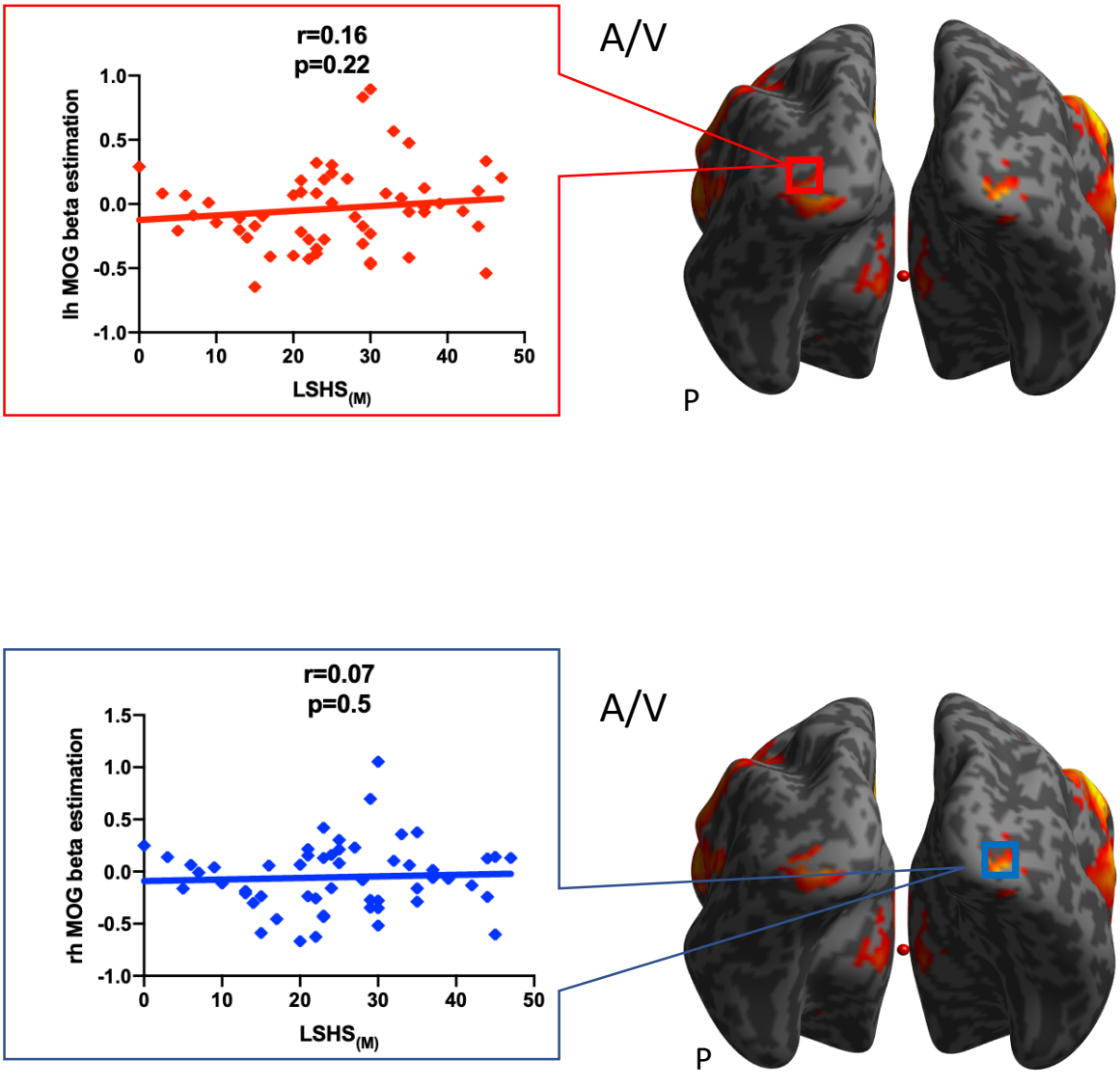

Figure 5.10: shows a positive correlation noticed between the $LSHS_{(M)}$ scores and left middle occipital gyrus activation (red) in audio/visual task. Furthermore, a positive correlation between the $LSHS_{(M)}$ scores and right middle occipital gyrus activation (blue) in the audio/visual task.

5.6.2 Inhibition

The previous sections considered relative activation in task-relevant areas to visual, auditory and audio-visual stimuli. The 'flip-side' of task relevant activation is inhibition in task-irrelevant areas.

5.6.2.1 Faces task (inhibition)

A significant positive correlation between the $LSHS_{(V)}$ score and activation in right superior temporal gyrus (STG) was found for the face recognition task, Figure 5.11. Further correlations between hallucination proneness scales ($LSHS_{(M)}$, $LSHS_{(A)}$, $LSHS_{(V)}$) and brain activation in language areas (bilateral TTG, bilateral STG and bilateral MTG), however, were not significant. All correlation results are shown in appendix C5-1, C5-2, C5-3.

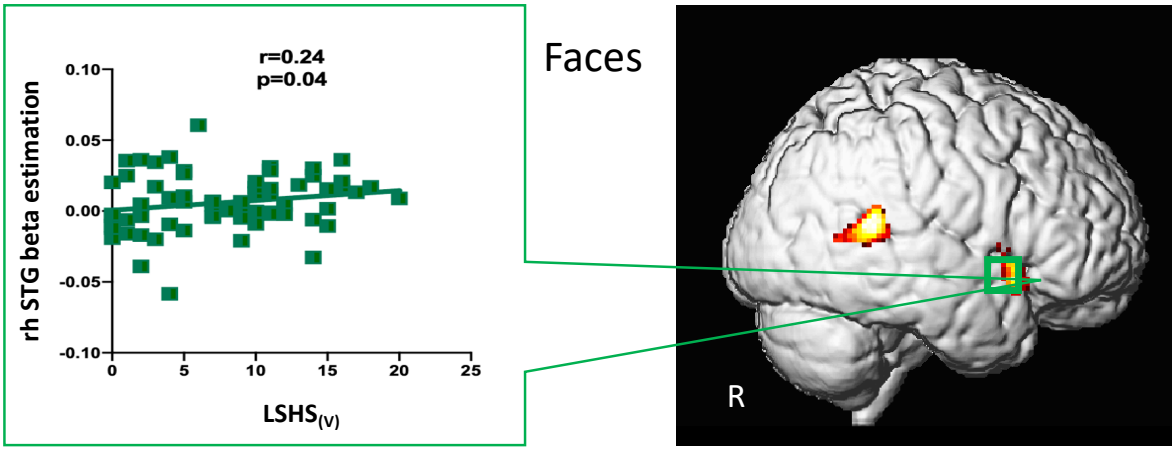

Figure 5.11: A significant positive correlation was shown between $LSHS_{(V)}$ scores and anterior (this is what the image suggests) right superior temporal gyrus (STG) activation in the faces task at $p<0.05$.

5.6.2.2 Audio/Visual (inhibition)

There was a significant positive correlation between $LSHS_{(A)}$ scores and right IFG activation (Figure 5.12), right superior temporal gyrus STG activation (Figure 5.13) and right middle temporal gyrus MTG (Figure 5.14) with in audio/visual task. Furthermore, a positive

correlation was revealed between language area activation (TTG, STG, MTG and MFG) and hallucination proneness scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) appendix C6-1, C6-2 and C6-3.

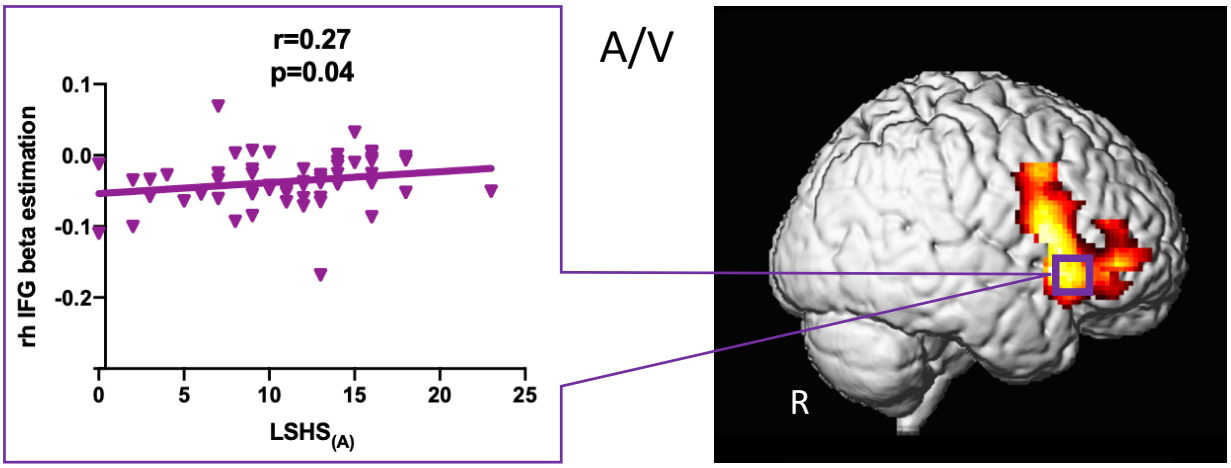

Figure 5.12: A significant positive correlation was shown between $LSHS_{(A)}$ scores and right inferior frontal gyrus (IFG) activation in the audio/visual (A/V) task at p<0.05.

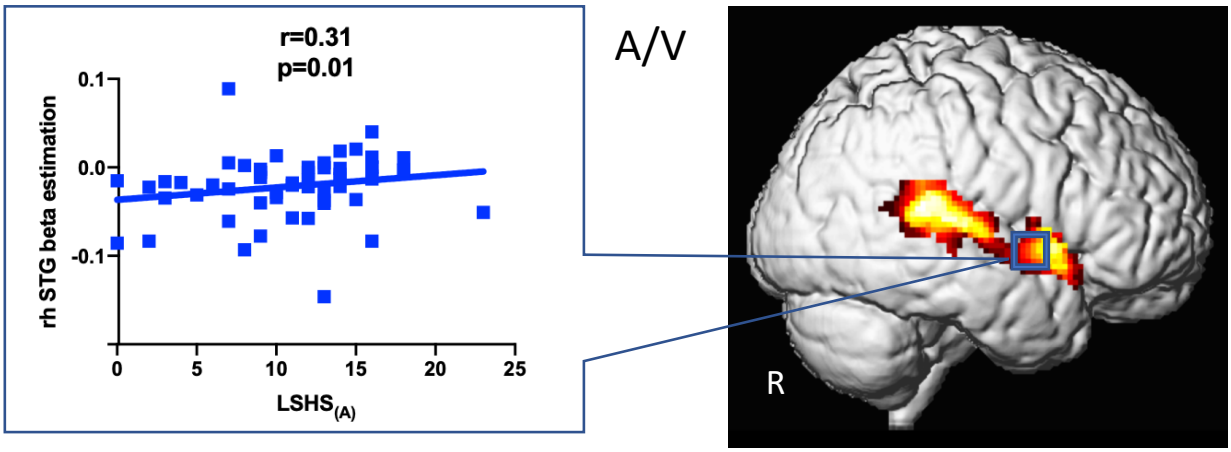

Figure 5.13: A positive correlation was shown between $LSHS_{(A)}$ scores and right superior temporal gyrus (STG) activation in the audio/visual (A/V) task at p<0.05.

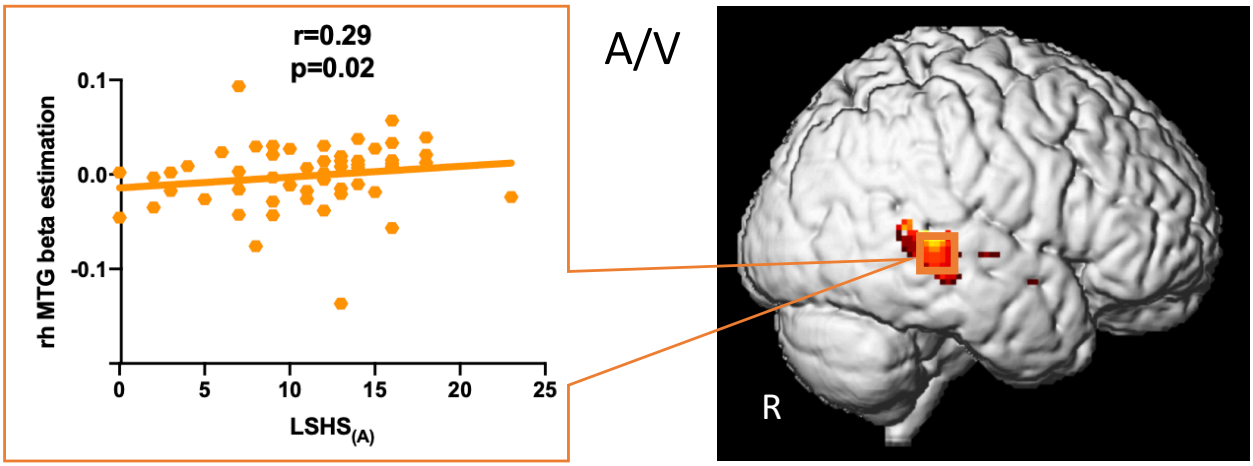

Figure 5.14: A significant positive correlation was shown between $LSHS_{(A)}$ scores and right middle temporal gyrus (MTG) activation in the audio/visual (A/V) task at p<0.05.

Interim summary

A prevailing explanation for hallucinations is a failure to inhibit task irrelevant areas. The data supports this view for activity in language related areas while participants perform visual tasks (face processing and visual signal detection). Activity in middle and superior temporal areas as well as inferior frontal areas is relatively larger in participants with higher $LSHS_{(A)}$ scores than for those with lower scores. This effect is limited to the right-hand side and the opposite effect, more excitation in these areas for high scorers, is not seen for any of the tasks.

5.6.3 Lateralization Index (LI)

Lateralisation differences have also been proposed as a possible explanation for hallucinatory experience. The following sections test whether the lateralisation index co-varies with $LSHS_{(M)}$ scores in our large, healthy participant pool.

5.6.3.1 Voice condition (LI)

The lateralisation index, computed as the proportion of voxels active on within the left and right IFG (and other areas) was correlated with ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scales in appendix C7-1, C7-2, C7-3. None of these measures were significantly correlated. Figure 5.15 and 5.16

show example data sets for the voice comprehension condition in the IFG and TTG. The full set of correlation results are given in appendix C7-1, C7-2, C7-3. An example scatter plot for the data in Figure 5.15 shows no correlation between the lateralization index of the IFG activation in voice condition and $LSHS_{(M)}$ scores. In addition, an example scatter plot for the data in Figure 5.16 shows no correlation between the lateralization index of the TTG activation in voice condition and $LSHS_{(M)}$ scores.

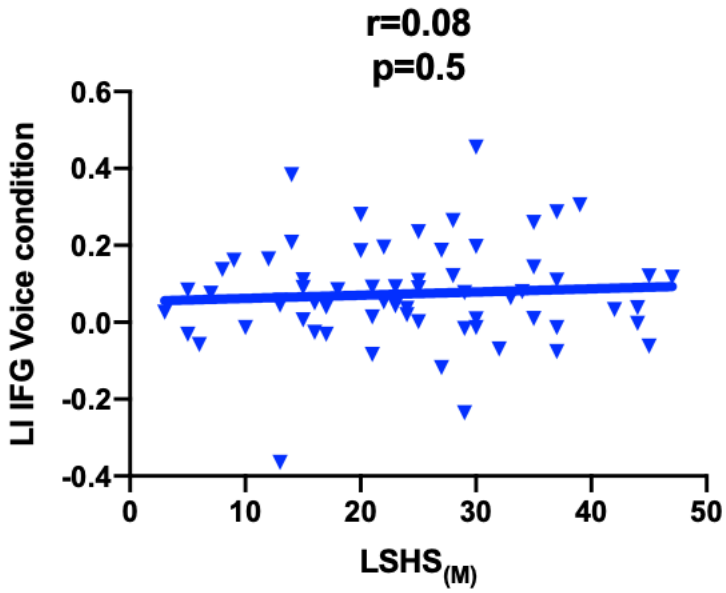

Figure 5.15: Scatter block showing the correlation between $LSHS_{(M)}$ and the LI computed for IFG on the basis of all voxels in the area activated at $p_{FWE} < 0.05$ during the voice comprehension task.

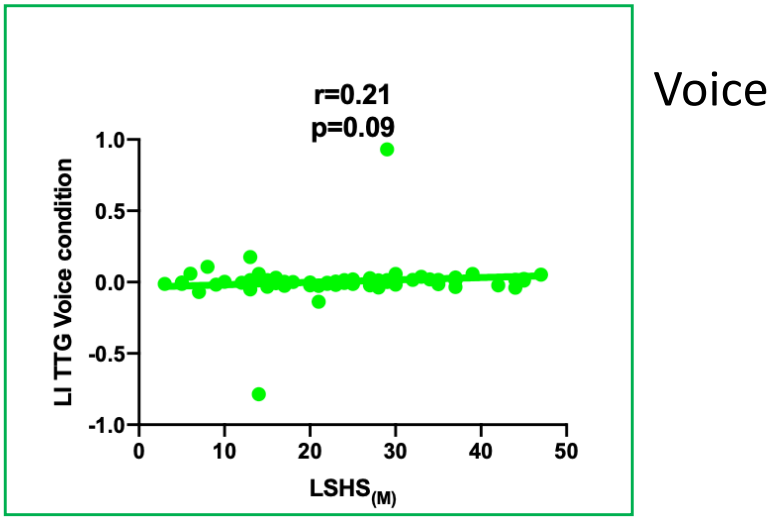

Figure 5.16: Scatter block showing the correlation between $LSHS_{(M)}$ and the LI computed for TTG on the basis of all voxels in the area activated at $p_{FWE} < 0.05$ during the voice comprehension task.

5.6.3.2 Text condition (LI)

The lateralisation index, computed as the proportion of voxels active on within the left and right IFG (and other areas) was correlated with ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scales in appendix C8-1, C8-2, C8-3. None of these correlations were significant ($p_{unc} < 0.05$). An example scatter plot for the data in Figure 5.17 shows no correlation between the lateralization index of the IFG activation in text condition and $LSHS_{(M)}$ scores. Furthermore, Figure 5.18 shows no correlation between the lateralization index of the TTG in text condition and $LSHS_{(M)}$ scores.

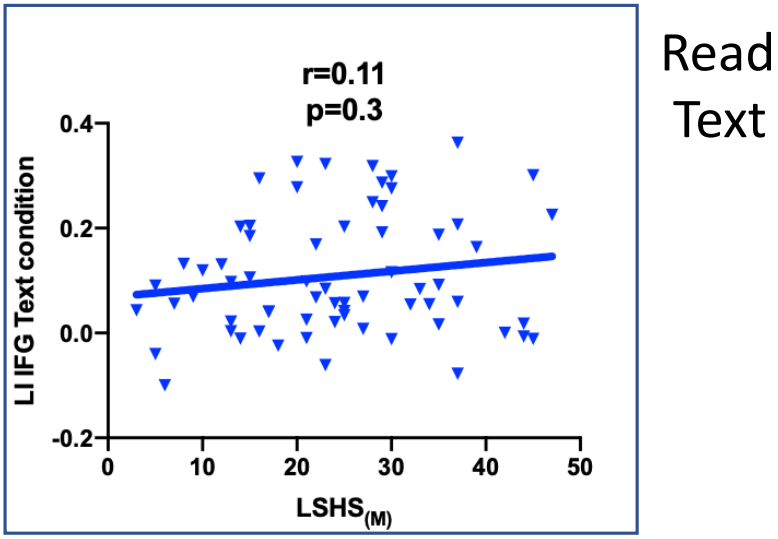

Figure 5.17:. Scatter block showing the correlation between $LSHS_{(M)}$ and the LI computed for IFG on the basis of all voxels in the area activated at $p_{FWE} < 0.05$ during the text comprehension task.

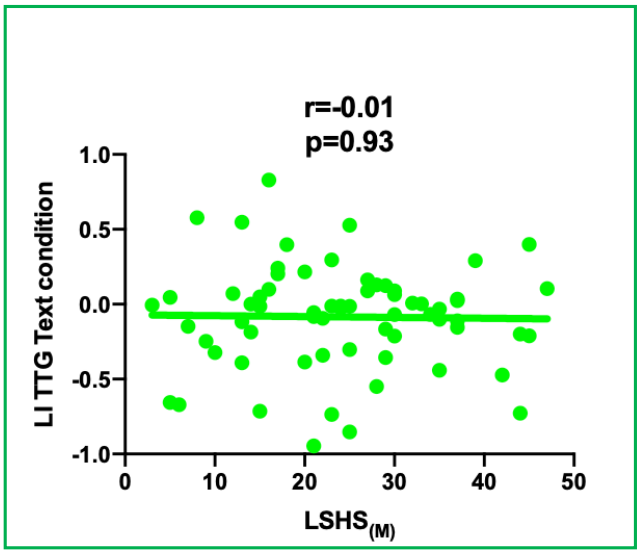

Figure 5.18: Scatter block showing the correlation between $LSHS_{(M)}$ and the LI computed for TTG on the basis of all voxels in the area activated at $p_{FWE} < 0.05$ during the text comprehension task.

5.7 Discussion

This chapter examined the correlation between the hallucination severity scales ($LSHS_{(M)}$, $LSHS_{(A)}$, $LSHS_{(V)}$) scores and the brain activity in the three fMRI tasks; voice and text comprehension, face recognition and (audio)visual (A/V) signal detection in task-relevant areas. A region of interest analysis was carried out to correlate activation levels with $LSHS_{(M)}$ scale data. These ROIs were computed from the task specific activation maps. To limit the number of possible comparisons, ROIs were limited to regions that have previously been identified in patients with hallucinations.

The selected ROI for the voice and text comprehension tasks consisted of IFG, MFG, SFG, TTG, STG, MTG, ITG and Insula. ROIs for the face detection and (audio) visual detection tasks were Fusiform Cortex, MOG and IOG.

In addition, the correlation between individual hallucination proneness cores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and activation in task-irrelevant brain regions was tested for the faces recognition and (audio)visual detection task. Finally, lateralization index (LI) was tested against $LSHS_{(M)}$ scores in language areas (IFG, MFG, TTG, STG, MTG and ITG) for the voice and text tasks.

The hypothesis that was tested was that activation patterns in healthy participants should lie on a continuum with the effects seen in patient populations, and therefore predict $LSHS_{(M)}$ scores.

This study provides two main findings:

1) Task evoked activity and lateralisation indices in task relevant areas were not correlated with hallucination scores – for any of the tasks, any of the brain regions or any of the three ($LSHS_{(M, A \text{ and } V)}$) scores tested. The data therefore does not provide positive evidence for the continuum hypothesis (Baumeister et al., 2017).
2) Activation is task irrelevant, language related areas, in contrast, was positively correlated with ($LSHS_{(A \text{ and } V)}$) scores in the right middle temporal, superior temporal cortex and inferior frontal cortex. This finding is consistent with predictions of models that postulate an inhibition deficit as a potential cause of hallucinations.

In the voice condition, none of the correlations between activation and $LSHS_{(M)}$ scores were significant. However, the correlation was toward a positive between ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores and the voice task in the middle frontal gyrus (MFG). The results of my study indicate that the high hallucination proneness participants exhibited more brain activation compared to the low hallucination proneness in an area involved in language. This data is consistent with a previous study (Braver et al., 1997). Moreover, a positive correlation was shown between the inferior frontal gyrus activation bilateral and hallucination severity scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$). However, contrasts with others (Dierks et al., 1999; Fitzgerald et al., 2007; Holmes et al., 2005; Shergill et al., 2000; Van De Ven et al., 2005; Waters, 2013). This result is consistent with previous studies (Frith et al., 1995; McGuire et al., 1996). Interestingly, some studies have also identified that the prefrontal cortex is involved in impaired context processing (Barch et al., 2001; MacDonald & Carter, 2003; Perlstein et al., 2003). Moreover, a positive correlation between hallucination severity ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores and bilateral (STG and MTG) activations in the voice condition. However, it is not significantly correlated. Gallinat et al., 2002 reported the opposite result, which is reduced activation in the superior temporal gyrus in a patient with AVH. Interestingly, Kuhn & Gallinat, 2012 noticed alteration of the activity in the temporal lobes (STG and MTG) to patients experience AVH. Moreover, Plaze et al., 2006 reported negative correlation between hallucination severity scale and brain activity in the left superior temporal gyrus during

listening to sentences. A positive correlation revealed between insula hallucination and the hallucination severity ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$). Hoffman et al., 2008 reported the insula was near a place activation at the inferior frontal gyrus, which extended the activation to the insula later. Wise et al., 1999 reported activation in the insula was correlated with the joint of speech. On the other hand, Giraud et al., 2004 argued that the activation in the insula before hallucination leads to inner speech.

In the text block, none of the correlations between activation and $LSHS_{(M)}$ scores were significant. However, a positive correlation between $LSHS_{(M)}$ scores and the inferior frontal gyrus was identified. Consistently, the inferior frontal gyrus has been shown to be involved in hallucinations (Van Lutterveld et al., 2013) and the results of this study was in line with previous reports (Fitzgerald et al., 2007). Moreover, the hallucination severity ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) positive correlated with brain activation in the superior temporal gyrus and superior frontal gyrus. These in line with (Wang et al., 2008; Price., 2000) which reported that during visual reading the superior frontal gyrus and superior temporal gyrus were activated. In addition, a positive correlation found between ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) insula during reading text. Interestingly, McGuire et al., 1996 argued that reading with distorted feedback of the subject increase activation in insula. Which paly role in misattribution the of non-self source. Those activation in the regions (superior temporal gyrus, inferior frontal gyrus and insula) associated with hallucination during reading (inner speech) may lead to failure on source monitoring. Moreover, Daprati et al., 2007 argued that hallucination is triggered by deficiencies in the immediate distinction between self-generated and external induced.

In the faces task, none of the correlations between activation and $LSHS_{(M)}$ scores were significant. The faces task provides evidence for the involvement of visual areas in the generation or experience of visual hallucination in high hallucination proneness. The severity hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) correlated with faces activation and a positive correlation in the visual cortex (middle occipital gyrus and superior occipital gyrus) areas was identified, however, it does not reach to significant. This is in line with Zmigrod et al., 2016 results claimed, visual hallucination linked to visual cortex activity. Also, the Precuneus was also identified to be positively correlated with $LSHS_{(M)}$ scores. The Precuneus has been reported to be involved in the integration of visuospatial imagery, processing of self-centred mental imagery strategies and to separate body image from external space;

impairments in which results in the development of hallucinations (Pagonabarraga et al., 2014). Studies found that Precuneus was activated during visual hallucinations (Silbersweig et al., 1995) and that patients with hallucinations demonstrated increased activation in the Precuneus (Oertel et al., 2007); in line with the findings from this study. A positive correlation in the faces task was identified between hallucination severity scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and the fusiform activation, indicating that the participants in the high hallucination proneness group exhibited high activation in the Fusiform. This consistent with (Kensinger and Schacter, 2005) results, and this brain region (Fusiform) was also associated with visual imagery. Furthermore, visual hallucination may consist of the reoccurrence of visual memory-based mental images misinterpreted (Barnes, 2015; Bentall, 1990).

In the audio/visual task, none of the correlations between activation and $LSHS_{(M)}$ scores were significant. However, a positive correlation in the audio/visual (A/V) task was identified between hallucination severity scales scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and the visual cortex (Precuneus, SOG and MOG), indicating that the participants in the high hallucination proneness group exhibited high activation in the visual cortex. The result is consistent with Daselaar et al., 2010 finding. The result is in line with (Ishai et al., 200; Kosslyn, 2000; Suchan & Ya, 2002) finding, greater activation in Precuneus. The Precuneus involving is visuospatial working memory or at tension (Culham & Kanwisher., 2001).

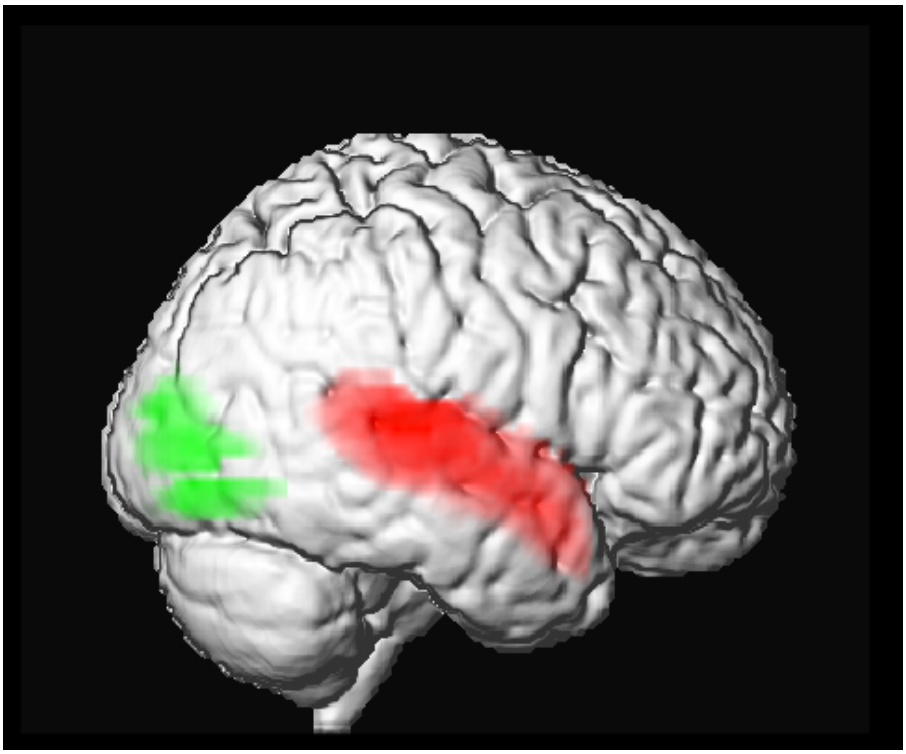

Figure 5.19: Render projection of brain regions expected activation during visual task (faces and A/V). Irrelevant task regions in the temporal lobe, expected to see deactivation (red). Relevant task regions in the occipital lobe, to see activation (green).

In the visual tasks (faces and A/V) stimulus, Figure 5.19 shows the expectation for the activation in irrelevant and relevant brain regions. However, Irrelevant task activation (temporal regions) in the faces and audio/visual (A/V) tasks positively correlated with hallucination severity scales scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$). A positive correlation noticed between $LSHS_{(A)}$ scores and right superior temporal gyrus in faces task. In addition, a positive correlation noticed between $LSHS_{(A)}$ scores and (right inferior frontal gyrus, right superior temporal gyrus and right middle temporal gyrus) activation in audio/visual task. The results in line with Waters et al., 2003 findings. Moreover, the results replicate Badcock et al., findings, there is a relation between planned inhibition struggles and hallucination experiences. Healthy prone to hallucinations shows challenges in the volunteer inhibition the currently irrelevant activation. In contract, previous studies suggested that these participants during the visual task tried to ignore or deactivate irrelevant task activation in the temporal lobe (Ciaramitaro et at., 2007; Johnson & Zatorre, 2005). Consequently, the activation in the temporal lobe, which is involved in language, was minimal. A previous study has suggested that reduced activity in the temporal lobe is the result of the opposite relationship between activity in prefrontal and medial temporal cortices (Kim et al., 2003).

The findings of the experimental fMRI study have revealed that the language related regions (i.e IFG and STG) have reduced overall functional brain asymmetry. This study result that decrease lateralization in healthy hallucination proneness subjects is due to a related increase in the right hemisphere is consistent with finding from other in AVH patients (Sommer et al., 2001b; Sommer et al., 2003). (Annett, 1992) claimed that right hemisphere growth of language related regions is responsible for the normal cerebral asymmetry in healthy subjects. It was therefore suggested to experiences an abnormality in this right hemisphere change linked to psychosis in patients (Crow et al., 1996). (Leitman et al., 2007) suggested increase right side activation within the group of schizophrenia during language task can also reflect known abnormalities prosodic process. This argument also explains the positive correlation between $LSHS_{(A)}$ scores and irrelevant task (inhibition) in audio/visual task in the right (STG and MTG).

The results are inconsistent with the first hypothesis. none of the correlations between activation and $LSHS_{(M)}$ scores were negatively significant as predicted by the continuum theory. However, none of the correlations were significant. The results instead, show a positive correlation between hallucination severity scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and relevant activation tasks in the (voice & text, faces and audio/visual), however, it does not reach significant. Temporal region (TTG, STG and MTG) activation in the voice & text task was positively correlated with hallucination proneness, and in occipital regions (MOG and SOG) and fusiform cortex, fMRI activation in the faces and audio/visual tasks was also positively correlated with hallucination proneness.

The results are inconsistent with the second hypothesis (inhibition). The results for the second hypothesis show a positive correlation between the hallucination severity scales and irrelevant (inhibition) in the language-related regions in the faces and audio/visual tasks. The results show a positive correlation between hallucination severity scores and temporal regions (TTG, STG and MTG) in the faces and audio/visual tasks.

The results are inconsistent with the third hypothesis. The results show no significant correlation between the lateralization index in the language-related regions (IFG and TTG) and the ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores.

5.8 Conclusion

In conclusion, three fMRI tasks were completed in this study, including the (voice & text), faces and visual stimuli tasks. The $LSHS_{(M)}$ scores were correlated to brain activity during relevant tasks. none of the correlations between activation and $LSHS_{(M)}$ scores were significant. In the voice blocks, this study identified a statistically a positive correlation between $LSHS_{(M)}$ scores and brain activity in the language related areas. In the text blocks, a statistically a positive correlation was identified between $LSHS_{(M)}$ scores and brain activity in related language areas, however none of the correlation reaches to significant. Furthermore, in the faces and visual stimuli tasks $LSHS_{(M)}$ scores were positively correlated with brain activation in the areas related to visual cortex, also, none of the correlation reaches to significant. However, in faces task (irrelevant), right STG was positive correlated with scores on the $LSHS_{(A)}$. Moreover, a positive correlation between correlation noticed between

irrelevant task activation and hallucination severity scales. Together, these data have added to our current understanding of how hallucination proneness in the general population is correlated with brain activation. The results of the lateralization index (LI) show no significant correlation in the in the language related brain activation in the voice and text task with hallucination scales.

Chapter 6

Links Between Hallucination Proneness and Brain Microstructure

6.1 Introduction

Hallucinations are the perception of sensory events in the absence of external stimuli, and importantly, these experiences are perceived as 'real' by the individual (Mondino, Dondé, Lavallé, Haesebaert, & Brunelin, 2019). The experience of hallucinations is a common symptom of schizophrenia and can affect all the senses. Auditory verbal hallucinations (AVH) are defined as the perception of voices in the absence of external stimuli (McCarthy-Jones, Thomas, et al., 2014), occur in in 60-80% of patients (Leroux, Delcroix, & Dollfus, 2017) and may present as one voice, several voices, coming from the environment or perceived to be coming from inside the patient's head (Nathou, Etard, & Dollfus, 2019). Compared to AVH, visual hallucinations (VH) are less commonly observed in schizophrenia patients, occurring in 23-31% of patients (McCarthy-Jones, Thomas, et al., 2014). It follows that fewer studies have investigated the types and neurobiological mechanisms underlying VH in schizophrenia patients (Toh, McCarthy-Jones, Copolov, & Rossell, 2019), although it has been suggested that these develop due to mental images being more abundant or vivid in these patients and therefore are more easily confused with perceived imagery (Brébion, Ohlsen, Pilowsky, & David, 2008; Johnson, Hashtroudi, & Lindsay, 1993). AVH and VH are often experienced as negative by the patient and can be very disabling (Chouinard et al., 2019; Larøi et al., 2019; Leroux et al., 2017).

Although commonly associated with schizophrenia, healthy individuals can also experience AVH (Daalman et al., 2011; Toh et al., 2019). The finding that hallucinations are commonly experienced in healthy individuals has led to the continuum hypothesis, described in detail in Chapter 3, which posits that the underlying cause(s) of hallucinations are the same for healthy voice hearers and patients; the key difference between the two groups lies in the severity of the hallucinatory experience. If the experience is caused by a common mechanism, and if this mechanism manifests itself in neural measures that differentiate healthy controls from

patients, then these measures should also be predicted by hallucination proneness measures, like the LSHS scale, discussed in detail in Chapter 3.

To determine the structural and functional central nervous system (CNS) abnormalities that may contribute to the development of AVH, many studies have employed a plethora of neuroimaging techniques (Leroux et al., 2017). These studies have generated a wealth of data that has led to the current consensus hypothesis in the field: AVH primarily develop through altered functional connectivity between speech-related areas and other areas in the CNS, as well as focal structural alterations to speech-related areas of the brain (Steinmann, Leicht, & Mulert, 2014). Evidence for gross structural alterations and for functional activation differences have been discussed in the two previous chapters. This chapter focuses on Diffusion Tensor Imaging (DTI), an imaging paradigm that measures the degree and direction of local water diffusivity in the brain.

DTI is a neuroimaging technique that is widely used to examine microstructural white matter (WM) abnormalities (Lee et al., 2013). When a chosen gradient field is applied to a specific area in the brain for imaging, this area of investigation will be sensitive to the diffusion of water molecules in the direction of the gradient field (Jellison et al., 2004). The directionality of diffusion is determined by the anatomical structure of the brain tissue: myelin sheaths and axonal membranes, for example, limit water diffusion orthogonal to the direction of major fibre tracts, so that the principal diffusion axis follows that of major fibre tracts. The degree of free water in neural structures directly determines the degree of diffusion that is possible: water diffuses easily and isotropically in ventricles, but diffusion is limited in tightly packed tissue areas.

DTI estimates water diffusivity in neural tissue along three orthogonal axes (Figure 6.1) and is a reliable indicator of microstructural changes (Zatorre et al.,2012; Sampaio-Baptista & Johansen-Berg et al., 2017; Cao et al., 2016). Water molecule diffusivity in a parallel direction to the white matter tracts (λ1) is detectable by a DTI marker called axial diffusivity (AD). AD decreases have been linked to axonal injury while brain maturation leads to increases in AD (Feldman et al., 2010; Alexander et al.,2011). The average of the two perpendicular diffusivity directions (λ2 and λ3) is radial diffusivity (RD) (Acosta-Cabronero et al., 2010). RD is a sensitive measure of myelination and of changes or group differences in the axonal diameters or

density (Cao et al., 2016; Choi et al., 2015). The average amount of water diffusion across all three major axes in a voxel is defined as the mean diffusivity (MD) (O'Donnell et al., 2011), see Figure 6.1.

The fractional anisotropy, or FA, is a summary measure of microstructural integrity that is highly sensitive to neuroplastic change (O'Donnell et al., 2011). The measure describes the asymmetry in diffusion along the major axis relative to the other two axes and ranges from 0 in voxels with equal (isotropic) diffusion in all three major directions to a maximum of 1, where diffusion is only possible in the AD direction.

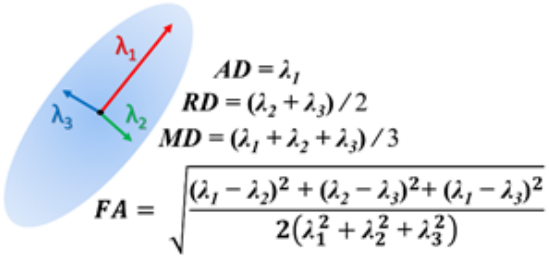

Figure 6.1 Water diffusivity measures from DTI: the diagram shows the water diffusivity in a voxel relying on neurons' axonal directions, axial diffusivity (AD) which is parallel to the axonal direction, radial diffusivity (RD) which is perpendicular to the axonal direction, and mean diffusivity.

DTI parameters reflect microstructural alterations induced by external drivers, such as medication (Egger et al., 2016) development and ageing (Madden et al., 2009) as well as practice (Sampaio-Baptista & Johansen-Berg et al., 2017). Increasing FA or decreasing MD, for example, have been associated with neurogenesis or myelination during training (Sampaio-Baptista & Johansen-Berg et al., 2017; Madden et al., 2009). Similarly, training-induced changes in AD or RD were suggested as indices of myelination or pre-myelination stages of microstructural alteration (Cao et al., 2016; Egger et al., 2016). DTI measures are also commonly used in differential diagnosis of a range of conditions ranging from oncology (review: Svolos et al., 2014) where structural changes are obvious, via diseases such as Parkinson's disease (review: Cochrane and Ebmeier, 2013) to areas such as ADHD and autism (review: Tuarines et al., 2012). It is therefore not surprising that DTI has been applied to elucidate the cause of hallucinations.

Links between DTI parameters, in particular FA measures, and schizophrenia are well established. Parnanzone et al. (2017) for example, in a recent systematic review, identify white matter alterations in schizophrenia patients relative to controls, but also look at two relevant sub-groups, namely healthy participants with a high risk of psychosis and first-episode psychosis patients. Their principal conclusion is that, despite a high degree of variability in the areas where diffusivity measures were found, there is evidence of disruptions of white matter integrity in cortical brain regions, associative and commissural tracts. These differences are clearly visible in chronic schizophrenia patients where 36 out of 46 reviewed studies explicitly report an FA reduction, four show no differences and only one reports an FA increase. Reports of FA decreases are often accompanied by reports of diffusivity increases. While the 'direction of travel' is clear, it is very striking that the observed changes are distributed across a very wide range of brain regions. Many fibre tracts, in particular the corpus callosum, cingulum, uncinate, arcuate, longitudinal (inf and sup) and fronto-occipital fasciculus, but also cortical regions, especially the temporal and parietal cortex, are mentioned in multiple studies. Interestingly similar reductions in FA as seen in chronic patients were also seen in healthy high risk populations, lending support to Baumeister's continuum theory. Further support for the continuum model is provided by Daalman et al. (2016), who conducted a five-year follow-up study of over 103 healthy voice hearers and found that, over this period, five individuals with AVH (6.2%) developed psychosis and 32 (39.5%) required some form of mental healthcare. The nature of AVH did not change in 86.2% individuals and voice-related distress at baseline significantly predicted the need for mental healthcare. These findings are in stark contrast to data for their control group, where no-one developed psychotic symptoms, and the need for mental healthcare (n = 6, or 12.2%) was significantly lower.

The extensive evidence linking microstructural alterations, FA reduction and diffusivity increases to psychosis, as reviewed above, cannot be directly applied here because of the significant minority of psychotic patients who do not suffer from hallucinations, but a smaller number of studies that specifically look at hallucinatory experience, reviewed below, paint a similar picture.

In a meta-analysis of five studies, with 256 DTI data sets encompassing 106 patients with AVH and 150 healthy controls, Geoffroy et al. (2014) showed a reduced fractional anisotropy in the left arcuate fasciculus (AF) of hallucinators (hg = − 0.42; CI [− 0.69, − 0.16]; p < 10− 3) and conclude that disruptions of white matter integrity in the left AF bundle of schizophrenia patients are linked to AVH.

The meta-analysis of AF data included a study by Weijer et al. (2011), which considered three further fibre tracts, the cortico spinal tract, cingulum, and uncinate fasciculus, in 44 schizophrenia patients with chronic severe hallucinations and 42 controls. The patient group showed a general decrease in FA for all bundles which suggests a direct link between reduced fibre integrity in structures linking frontal and temporo-parietal language areas in schizophrenia patients with the experience of auditory verbal hallucinations. This finding is directly reflected in a simultaneous study by Catani et al. (2011), also included in Geoffroys meta-analysis, which adds insights into the laterality of the observed effects; specifically, patients with and without AVH showed reduced FA values in the AF compared with controls, but the difference in FA measures was greatest, and bilateral, in patients with AVH, while smaller and unilateral (left) reductions were seen in patients without AVH. More recent data (Chawla et al., 2019) using relatively large participant cohorts provide further evidence for significantly reduced FA in the bilateral superior longitudinal and arcuate fasciculi in patients with AH (n=30) compared to patients without AH (n=32) and healthy controls (n=30). No difference was observed in corresponding FA values between schizophrenia without AH and healthy controls. (Ashtari et al., 2007) reported reduced FA in the temporal and occipital regions within AVH patients.

The arcuate fasciculus is a major intra-hemispheric tract that connects temporal and parietal (language) areas with inferior-frontal (language) regions bilaterally and will be discussed in more detail in the next chapter. Other major fibre tracts, the interhemispheric auditory pathway (IAP) and corpus callosum (CC), which connect the two hemispheres, have been proposed as being involved in functional lateralisation differences (Chapter 5).

The interhemispheric auditory pathway crosses the hemispheres in the splenium of the corpus callosum and connects the left and right temporal cortices. Integrity loss, decreased FA and increased RD in this fibre bundle has been shown in patients with AVH relative to

patients without AVH and healthy controls in a number of studies (McCarthy-Jones et al. 2015; Curcic-Blake et al. 2015; Wigand et al., 2015; Leroux et al, 2017). These findings, however, are inconsistent with Mulert et al., (2012) who found no difference in the FA of the interhemispheric auditory fibres between schizophrenic patients and healthy controls. Mulert et al. (2012) also report that the subgroup of patients with AVH showed increased FA relative to patients without these symptoms ($p = 0.047$) and trendwise increased FA relative to healthy controls ($p = 0.066$). In addition, a trendwise correlation between FA values and AVH symptoms ($p = 0.089$) was found. A possible criticism of the study is that the patient number was very low (n=10), and there were only five patients in the VAH and no-AVH group, which makes the marginally significant statistics somewhat dubious. These findings are mirrored by Hubl et al. (2004) and Shergill et al. (2007) who also report *increased* FA in patients with hallucinations relative to patients without hallucinations and controls. Hubl et al. (2004) consequently use this data to explain hallucinations as an abnormal (increased) co-activation in regions related to acoustical processing of external stimuli.

Knoechel et al. (2012) compared DTI measures (FA and mean diffusivity) in patients with matching data from close relatives and controls (n=16,16,15). SZ patients and relatives had smaller corpus callosum (CC) volumes than controls, particularly in the posterior genu, isthmus and splenium. FA was reduced in patients and relatives in the whole CC, the inferior genu, the superior genu and the isthmus while MD values of the whole CC and the isthmus were higher in patients and their unaffected relatives. The authors make an explicit link between decreases in FA and increases in MD values as indicators of pathology: lower FA as a measure of loss of fibre integrity and increased MD as indicating decreased compactness and increased intercellular space. Finding that fibre integrity measures of family members sit between patients and controls suggests that there is at least some genetic component to these anatomical descriptors. Lee et al. (2013) report data that mirror Knöchelet al. (2012) for first-episode patients. They report that patients with schizophrenia showed lower FA values in the genu and body of corpus callosum, the internal capsule, the external capsule, the fornix, the superior, inferior fronto-occipital fasciculus, the cingulum, and the uncinate fasciculus compared with HC. There were no axial diffusivity differences, but increased MD and radial diffusivity were shown in most white matter regions. The authors correlated FA values with objective and subjective measures and found that the FA values of the right

inferior fronto-occipital fasciculus were positively correlated with positive symptoms, negative symptoms, and total correct items of the Wisconsin Card Sorting Test. FA values of the right external capsule also showed significant positive correlation with category completed scores of the WCST. These data suggest that there may be a direct link between microstructure and the severity of symptoms in patients.

Ćurčić-Blake et al. (2017) in their review summarise that, while the DTI data is not consistent, there is a general finding of increased FA in relevant fibre tracts in first-episode patients whereas, in chronic patients, decreased FA values relative to controls are seen. Table 6.1 summarises the literature reviewed. It is clear that the majority of studies, in particular those with larger participant numbers, find a reduction in FA and increase in a variety of diffusivity measures in the following main areas: Interhemispheric auditory tact, corpus callosum, superior longitudinal fasciculus, temporal lobe, uncinate fascicles, inferior occipitofrontal fascicle, temporal lobe and occipital lobe. These areas will be the focus of the data analysis.

Table 6.1: A summary of the literature reviewed

Region	Main finding	Author	Participants
Thalamus	MD↑	Spaletta et al., 2013	SZ-H = 15 SC-NH = 35
IAT	MD↑, FA↓ - SZ vs HC FA↓ - SZ-H vs SZ-NH	Leroux et al., 2017	SZ-H = 27 SZ–NH = 12 HC = 34
IAT	FA↓ SZ-H vs SZ-NH MD↑, FA↓ SZ-H in mid sagittal section	Wigand et al., 2015	SZ-H = 24 SZ–NH = 9 HC = 33
IAT	FA ↔ SZ vs HC FA↑ SZ-H vs SZ-NH	Mulert et al., 2012	SZ-H = 5 SZ–NH = 5 HC = 10
AF	FA↓ - SZ-H vs HC bilateral in SZ-H vs HC unilateral left in SZ-NH vs HC	Catani et al., 2011	SZ-H = 17 SZ–NH = 11 HC = 59
AF, UC CST Cingulum	FA↓ - SZ-H vs HC in all tracts	De Weijer et al., 2011	SZ-H = 44 HC = 42
CC, UC cingulum, FOF sup & inf	FA↓ - SZ-H vs HC in most WMR MD↑ in 'virtually' all WMR	Lee et al., 2013	FESZ = 17 HC = 17

CC	FA↓ - SZ-H vs HC in all CC MD↑ in all CC	Knöchel et al., 2012	SZ-H = 16 SZ–NH = 16 HC = 15
AF temp-parietal	FA↑ - SZ-H vs SZ-NH & HC	Hubl et al., 2004	SZ-H = 13 SZ–NH = 13 HC = 15
Cingulate gyri, UC, AF	FA↓ - SZ- vs SZ-NH & HC FA↓ - SZ-NH & HC in ALIC	Munoz Maniega et al., 2008	SZ = 22 HC–HR = 31 HC = 51
Temporal lobe (TL) Occipital lobe (OL)	FA↓ - SZ-H vs HC	Ashtari et al., 2007	SZ = 23 HC = 21

KEY: IAT: interhemispheric auditory tract, AF: arcuate fasciculus, CST: cortico spinal tract, UC: uncinate fasciculus, FOF: fronto-occipital fasciculus, ALIC: anterior limb of the internal capsules, SZ-H: schizophrenia patients with hallucinations, SZ-NH: schizophrenia patients without hallucinations, HC: healthy controls, FESZ: first-episode schizophrenia and HC-HR: healthy but high genetic risk.

Hypothesis:

On the basis of the literature reviewed above, it seems reasonable to accept that psychosis sufferers (with and without hallucinatory experiences) and, perhaps to a lesser degree, healthy hallucinators and high-risk groups, show reduced FA and increased diffusivity. The continuum model offers a possible explanation, but the data makes it impossible to differentiate whether the observed microstructural changes provide a single factor that explains psychosis *and* hallucinations or whether separate factors, perhaps mediating each other, explain mental distress and hallucinatory experience.

If a microstructural brain metrics predict hallucination proneness without other risk factors, then these measures should predict hallucination proneness in the healthy populations. The tested hypothesis, therefore, is whether $LSHS_{(M)}$ scores (see Chapter 3) are negatively correlated with FA measures (in other words, whether higher $LSHS_{(M)}$ scores predict lower FA values as seen in the patient population), and are positively correlated with diffusivity measures, specifically MD, RD and AD.

6.2 Methodology

This study was approved by the ethics committee at the University of Liverpool.

6.2.1 Participants

The Qualtrics website was used to create the $LSHS_{(M)}$ scale online and the link was distributed by email to students and staff at the University of Liverpool. More explanation about $LSHS_{(M)}$ and subscales ($LSHS_{(A)}$ and $LSHS_{(V)}$) is given in Chapter 3. A total of 75 participants were recruited to complete the $LSHS_{(M)}$ questionnaire, six of whom were inappropriate for MRI scanning for having a metal implant. Ninety-six participants were taken forward for MRI scanning. One of the participants that was included in the MRI scanning had to be excluded from further analyses, as the radiologists identified abnormalities in his scan. Finally, 68 participants were included in the data analysis, comprising 28 males and 40 females with an average age of 29.1 (SD=11.811; range, 19-66).

6.2.2 Parameters

The 3T Siemens Prisma scanner was employed in this study. DTI axial was taken. The parameters were 64 direction (voxel size = 2.5 x 2.5 x 2.5; TR =3200 ms, TE= 90.0 ms, FOV = 220 mm).

6.2.3 Image Pre-processing

6.2.3.1 FSL

DTI data were processed using FSL 5.0.11 (fsl.fmrib.ox.ac.uk/fsl/fslwiki) using the top-up programme to correct susceptibility induced distortions using images with opposite phase encoding. The eddy package was then used to correct images for eddy current distortion, movement, and motion-induced signal dropout. FA and diffusivity measures (MD, RD and AD) were then calculated with the DTIFIT.

6.2.3.2 ANTs

The Advanced Normalisation Tools (ANTs) toolbox was used to align the FSL output images for further analysis in preference to the more commonly used tract-based spatial statistic (TBSS) toolbox because it has been shown that the registration using ANTs is better than

FNIRT in TBSS (Schwarz et al., 2014). One common spatial average template was created in ANTs for all subjects in the study and all individual images were mapped onto this template. To improve the signal to noise ratio, a 5mm Gaussian filter was applied to smooth all images. Different masks relating to the auditory and visual hallucination areas were applied to extract the data. Employing the Harvard-Oxford Cortical structural atlas, the superior temporal gyrus anterior division and the superior temporal gyrus posterior division were both used. From JHU ICBM-DTI-81 White-Matter Labels, the corpus callosum, uncinate fasciculus right and left were selected. From JHU White-Matter tractography atlas, the superior longitudinal fascicle (left and right) and inferior fronto-occipital fasciculus left were used. From Juelich Histological atlas, the inferior occipital-frontal fascicle (left and right) and superior longitudinal fasciculus right and left were used. Though MNI Structural atlas, the temporal lobe and occipital lobe were selected. The data extracted by the mask was correlated with $LSHS_{(M)}$ score using GraphPad Prism Version 8.3.0 (328).

6.2.4 Correlation

GraphPad Prism version 8.4.0 was used to analyse the data extracted from the images.

6.3 Data Analysis

FA, MD, RD and AD values were extracted using the mask data. Spearman Rho was computed to evaluate any correlations between FA, MD, RD, AD values and $LSHS_{(M)}$ scores. Figure 6.2 shows the mask extracted from the brain areas of interest.

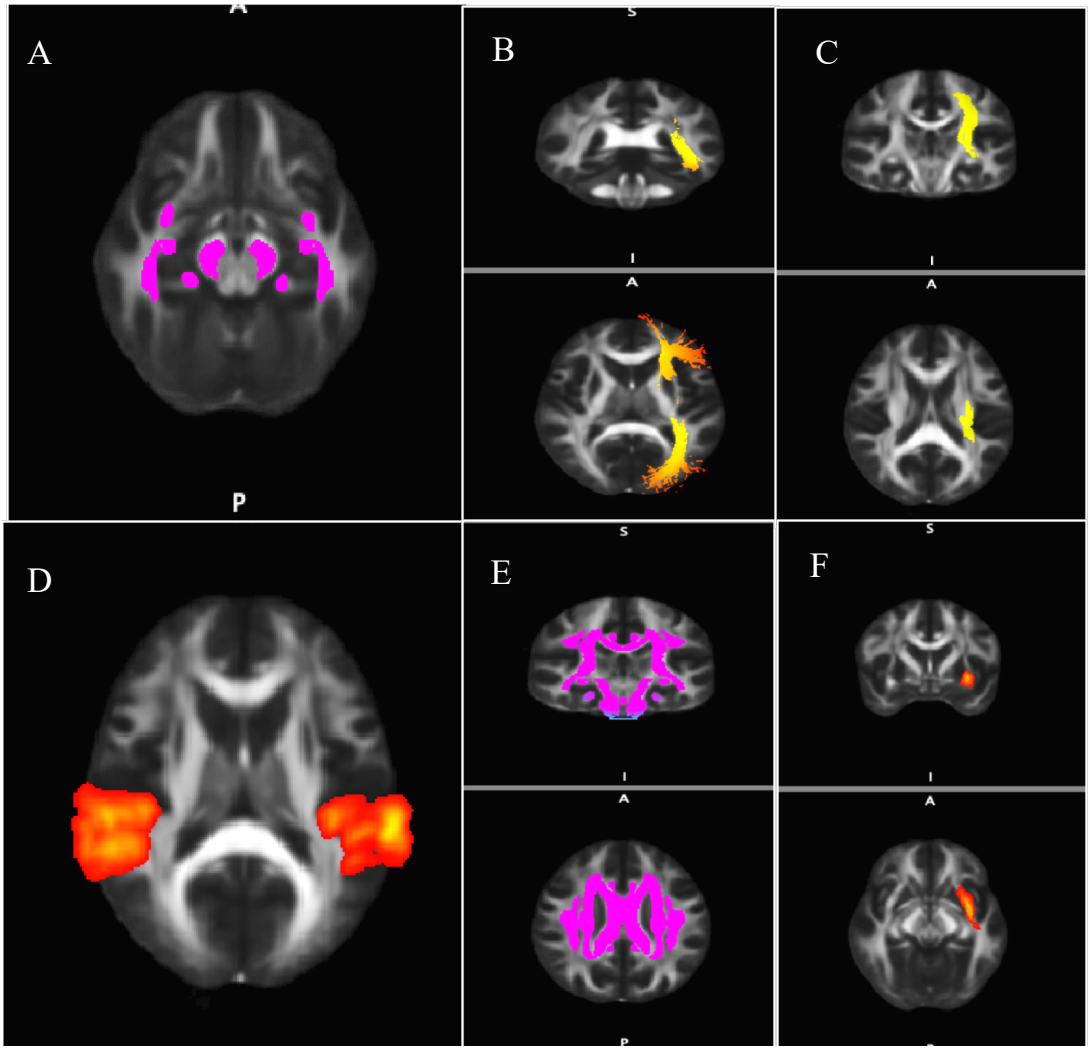

Figure 6.1: This is the FA map for one of the participants in this study showing the masks applied in the analysis: (A) Corpus callosum, (B) inferior_fronto_occipital fasciculus, (C) superior longitudinal fasciculus, (D) temporal lobe, (E) uncinate fascicles, inferior occipitofrontal fascicle side. These regions were chosen for analysis on the basis of the literature summarised in Table 6.1

6.4 Results

6.4.2 FA Correlation Results

6.4.2.1 FA Values Correlation with $LSHS_{(M, A \text{ and } V)}$

Nonparametric correlation tests were performed for the data extracted from the brain regions implicated in auditory and visual hallucinations with $LSHS_{(M)}$ as shown in Table 6.2, and there was no correlation between the mean FA value in any of the brain areas implicated in AVH or VH with $LSHS_{(M)}$ scores. Furthermore, no correlation was found between the mean FA and $LSHS_{(A)}$ and $LSHS_{(V)}$ scores.

Table 6.2: Correlation between $LSHS_{(M)}$ and FA values

Correlation	IAT	CST	CC	IFOF_lh	ILF_lh	ILF_rh	SLF_lh	SLF_rh	OL	STG	UF_lh	UF_rh	IOFF_lh	IOFF_rh	STG_A	STG_P	TL
Spearman r	0.04	0.01	0.04	0.12	0.09	0.1	-0.1	-0.08	-0.08	00.9	0.04	0.04	-0.004	0.02	0.04	0.08	0.02
P value	0.69	0.88	0.74	0.3	0.42	0.39	0.41	0.5	0.5	0.45	0.74	0.74	0.96	0.84	0.71	0.47	0.85

Key: IAT: interhemispheric auditory tract, CST: cortico spinal tract, CC: corpus callosum, IFOF: Inferior_fronto-occipital_fasciculus (rh & lh) right hemisphere and left hemisphere, ILF: inferior longitudinal fasciculus (rh & lh), SLF: superior longitudinal fasciculus (rh & lh), OL: occipital lobe, STG: superior temporal gyrus, UF: uncinate fascicles, IOFF: inferior_occipital_frontal fascicles, STG_A: superior_temporal gyrus anterior division, STG_P: superior_temporal gyrus posterior division and TL: temporal lobe.

6.4.3 MD Correlation Results

6.4.3.1 MD Correlation with $LSHS_{(M)}$

A nonparametric correlation test was performed between MD values and $LSHS_{(M)}$ scores (Table 6.3). The data extracted from the MD images showed a significant negative correlation with $LSHS_{(M)}$ scores in the inferior longitudinal fasciculus right side (ILF_rh) $P < 0.05$ (Figure 6.3), superior longitudinal fascicle rh (SLF_rh) $P < 0.05$ (Figure 6.4) and occipital lobe (OL) with $P < 0.05$ (Figure 6.5).

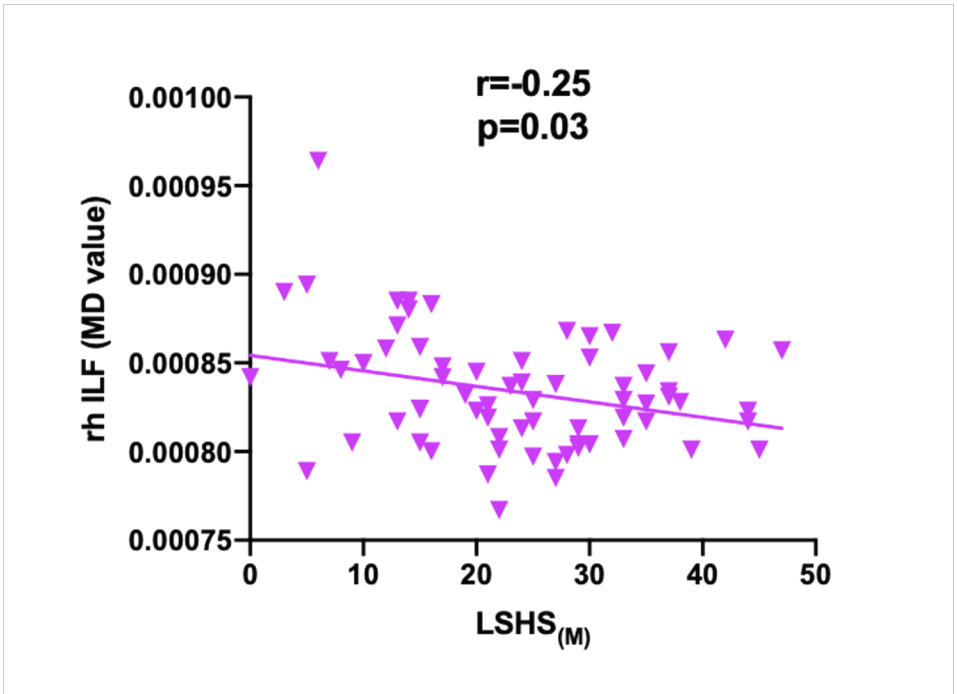

Figure 6. 2: MD value correlation between ILF_rh and $LSHS_{(M)}$ scores. ILF = inferior longitudinal fasciculus, LSHS = the Launay Slade Hallucination Scale.

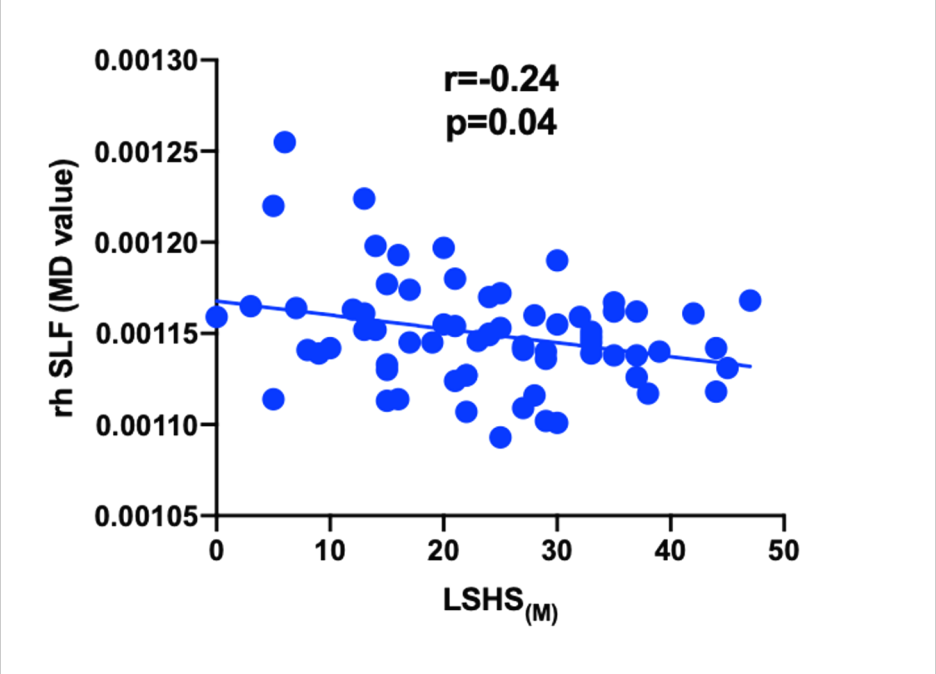

Figure 6. 3: MD correlation between $LSHS_{(M)}$ scores and SLF_rh. SLF = superior longitudinal fasciculus, LSHS = the Launay Slade Hallucination Scale.

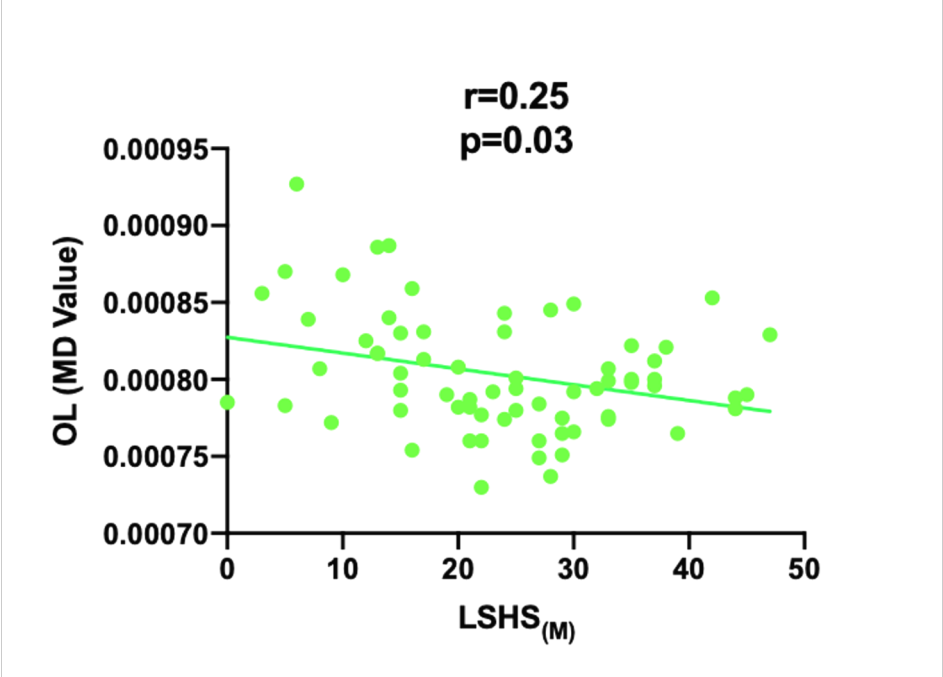

Figure 6. 4: MD correlation between OL and $LSHS_{(M)}$ scores. OL = Occipital Lobe, LSHS = the Launay Slade Hallucination Scale.

Table 6.3: Correlation between $LSHS_{(M)}$ scores and MD values

Correlation	IAT	CST	CC	IFOF_lh	ILF_lh	ILF_rh	SLF_lh	SLF_rh	OL	STG	UF_lh	UF_rh	IOFF_lh	IOFF_rh	STG_A	STG_P	TL
Spearman r	0.06	0.09	-0.1	-0.17	-0.2	-0.25	-0.2	-0.24	-0.25	-0.12	-0.1	-0.1	-0.11	-0.16	-0.11	-0.12	-0.11
P value	0.61	0.42	0.39	0.14	0.09	0.03	0.09	0.04	0.03	0.31	0.39	0.39	0.33	0.19	0.33	0.29	0.34

Key: IAT: interhemispheric auditory tract, CST: cortico spinal tract, CC: corpus callosum, IFOF: Inferior fronto-occipital fasciculus (rh & lh), ILF: inferior longitudinal fasciculus (rh & lh), SLF: superior longitudinal fasciculus (rh & lh), OL: occipital lobe, STG: superior temporal gyrus, UF: uncinate fascicles, IOFF: inferior occipital frontal fascicles, STG_A: superior temporal gyrus anterior division, STG_P: superior temporal gyrus posterior division and TL: temporal lobe.

6.4.3.2 MD Correlation with $LSHS_{(A)}$ Scores

A nonparametric correlation test was performed between MD values and $LSHS_{(A)}$ scores (Table 6.4). The results show significant negative correlation with $LSHS_{(A)}$ scores in the ILF (lh &rh), SLF (lh & rh) and OL.

Table 6.4: Correlation between $LSHS_{(A)}$ scores and MD values

Correlation	ILF_rh	ILF_lh	SLF_rh	SLF_lh	OL
Spearman r	-0.3096	-0.2499	-0.2406	-0.2406	-0.2613
p value	0.0102	0.0399	0.0481	0.0481	0.0314

Key: ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus and OL: occipital lobe.

6.4.3.3 MD Correlation with $LSHS_{(V)}$ Scores

A nonparametric correlation test was performed for the data extracted from the brain regions implicated in auditory and visual hallucinations and it was found that there was no correlation between the MD value and any of the brain areas implicated in AVH or VH and $LSHS_{(V)}$ scores.

6.4.4 RD Correlation Result

6.4.4.1 RD Correlation with $LSHS_{(M)}$

A nonparametric test was performed between RD values and $LSHS_{(M)}$ scores, shown in Table 6.5 below.

Table 6.5: Correlation between $LSHS_{(M)}$ scores and RD values

Correlation	IAT	CST	CC	IFOF_lh	ILF_lh	ILF_rh	SLF_lh	SLF_rh	OL	STG	UF_lh	UF_rh	IOFF_lh	IOFF_rh	STG_A	STG_P	TL
Spearman r	0.001	0.09	-0.07	-0.17	-0.21	-0.23	-0.14	-0.13	-0.25	-0.13	-0.07	-0.07	-0.11	-0.14	-0.13	-0.12	-0.13
P value	0.99	0.46	0.54	0.15	0.08	0.05	0.25	0.28	0.03	0.26	0.54	0.54	0.35	0.22	0.27	0.29	0.27

Key: IAT: interhemispheric auditory tract, CST: cortico spinal tract, CC: corpus callosum, IFOF: Inferior fronto-occipital fasciculus (rh & lh), ILF: inferior longitudinal fasciculus (rh & lh), SLF: superior longitudinal fasciculus (rh & lh), OL = occipital lobe, STG: superior temporal gyrus, UF: uncinate fascicles, IOFF: inferior occipital frontal fascicles, STG_A: superior temporal gyrus anterior division, STG_P: superior temporal gyrus posterior division and TL: temporal lobe.

This analysis revealed there to be a negative correlation (P<0.05) between RD values and $LSHS_{(M)}$ scores in the OL (Figure 6.6). No other significant correlations were observed.

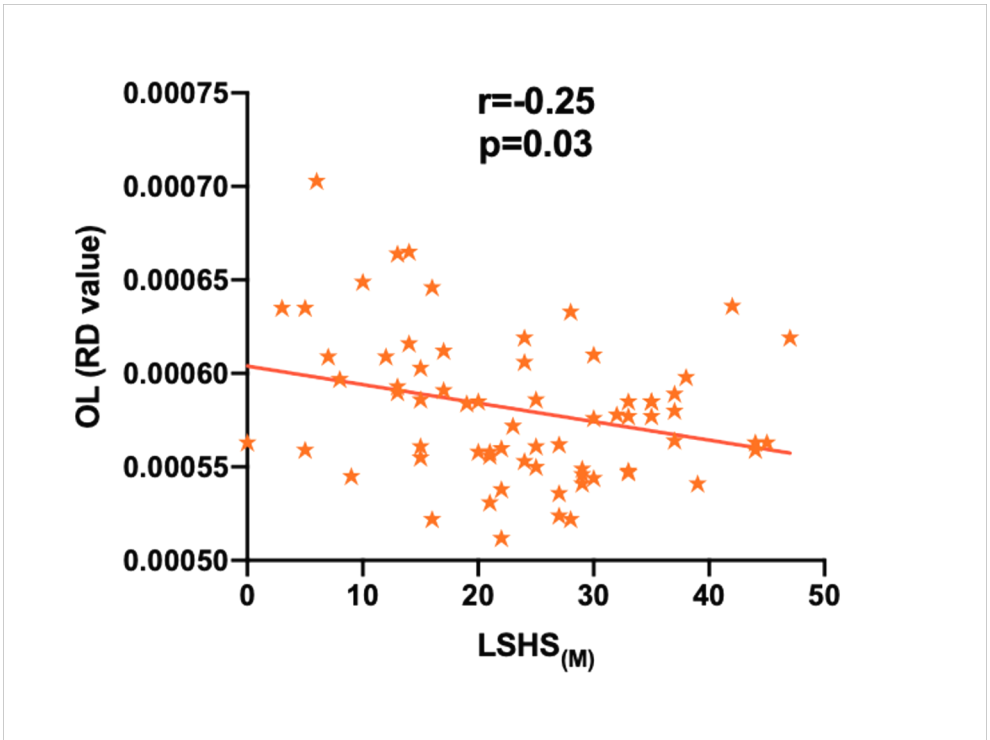

Figure 6. 5: Negative correlation between RD values in OL and $LSHS_{(M)}$ scores. OL = Occipital lobe, $LSHS_{(M)}$ = the Launay Slade Hallucination Scale Modified.

6.4.4.2 RD Correlation with $LSHS_{(A)}$ Scores

A nonparametric test was performed between RD values and the $LSHS_{(A)}$ scores, shown in Table 6.6. This analysis revealed there to be a negative correlation between RD values and the $LSHS_{(A)}$ scores in the IFOF_lh, ILF (lh & rh) and OL.

Table 6.6: Correlate of $LSHS_{(A)}$ score with RD

Correlation	$LSHS_{(A)}$ Vs. IFOF_lh	$LSHS_{(A)}$ Vs. ILF_lh	$LSHS_{(A)}$ Vs. ILF_rh	$LSHS_{(A)}$ Vs. OL
Spearman r	-0.2409	-0.2638	-0.2917	-0.2752
p value	0.0479	0.0297	0.0158	0.0231

Key: IFOF: inferior fronto-occipital fasciculus, ILF: inferior longitudinal fasciculus, SLF: superior longitudinal fasciculus and OL: occipital lobe.

6.4.4.3 RD Correlation with $LSHS_{(V)}$ Scores

A nonparametric test was performed between $LSHS_{(V)}$ score and RD values and revealed no correlation.

6.4.5 AD Correlation Result

6.4.5.1 AD Correlation with $LSHS_{(M)}$

The final correlation performed was between AD value and $LSHS_{(M)}$ scores, illustrated in Table 6.7.

Table 6.6: Correlation between $LSHS_{(M)}$ scores and AD values

Correlation	IAT	CST	CC	IFOF_lh	ILF_lh	ILF_rh	SLF_lh	SLF_rh	OL	STG	UF_lh	UF_rh	IOFF_lh	IOFF_rh	STG_A	STG_P	TL
Spearman r	0.15	0.12	-0.13	-0.17	-0.19	-0.27	-0.3	-0.24	-0.25	-0.1	-0.13	-0.13	-0.14	-0.19	-0.08	-0.12	-0.07
P value	0.2	0.33	0.25	0.16	0.11	0.02	0.01	0.04	0.03	0.38	0.25	0.25	0.25	0.1	0.47	0.32	0.51

Key: IAT: interhemispheric auditory tract, CST: cortico spinal tract, CC: corpus callosum, IFOF: inferior fronto-occipital fasciculus (rh & lh), ILF: inferior longitudinal fasciculus (rh & lh), SLF: superior longitudinal fasciculus (rh & lh), OL: occipital lobe, STG: superior temporal gyrus, UF: uncinate fascicles, IOFF: inferior occipital frontal fascicles, STG_A: superior temporal gyrus anterior division, STG_P: superior temporal gyrus posterior division and TL: temporal lobe.

The nonparametric test showed a significant negative correlation between AD values and $LSHS_{(M)}$ scores in the ILF rh ($p < 0.05$) (Figure 6.7 (A)), OL ($p<0.05$) (Figure 6.7 (B)), SLF left hemisphere (SLF lh) ($p < 0.05$) (Figure 6.8) and SLF rh ($p < 0.05$) (Figure 6.9).

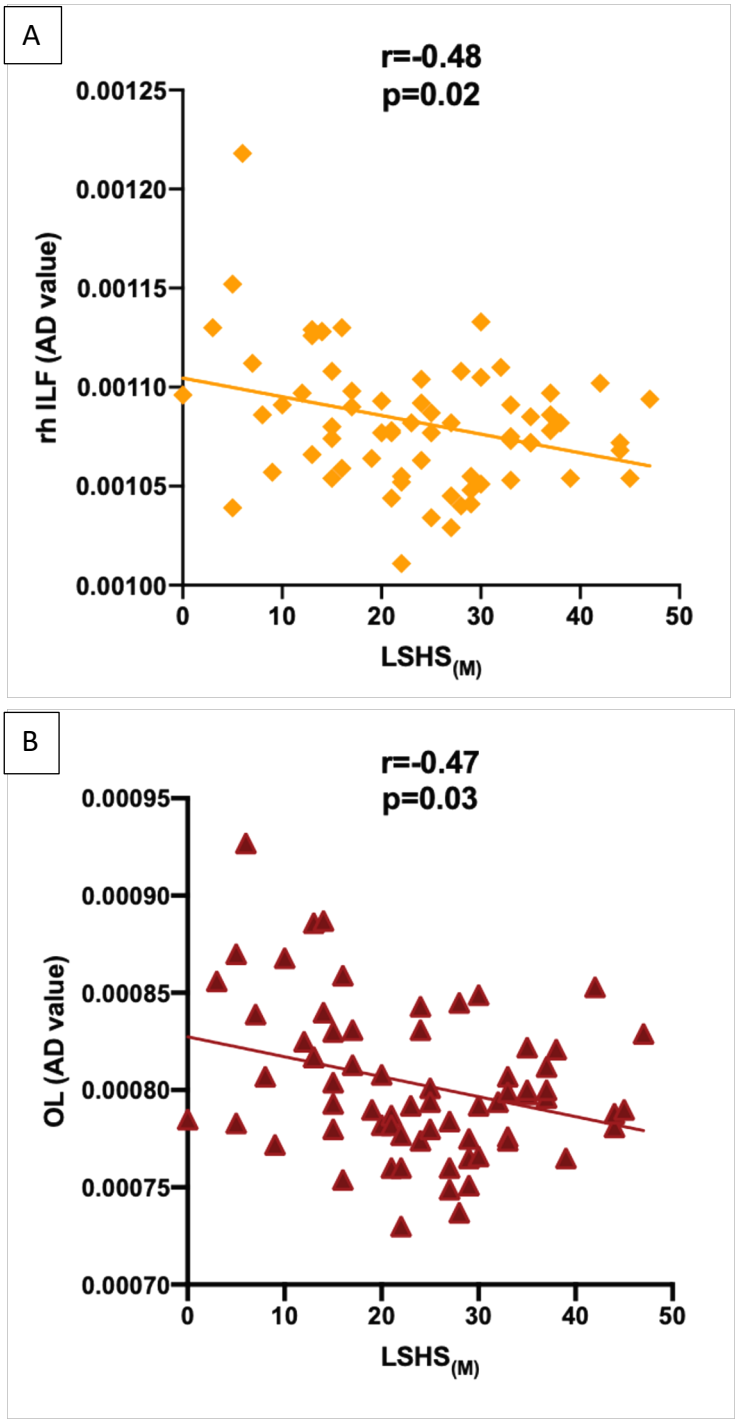

Figure 6.7: (A) AD correlation between ILF_RT AD values and $LSHS_{(M)}$ scores. (B) correlation between OL and $LSHS_{(M)}$ scores. ILF_RT = inferior longitudinal fasciculus, OL = Occipital Lobe, $LSHS_{(M)}$ = the Launay Slade Hallucination Scale Midified.

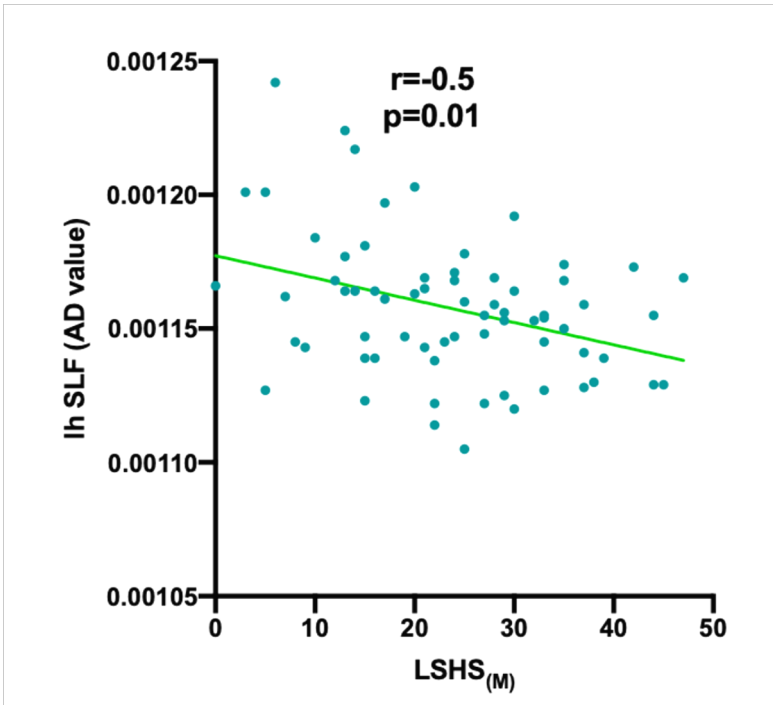

Figure 6. 8: AD correlation for $LSHS_{(M)}$ scores with lh SLF AD value. superior longitudinal fasciculus.

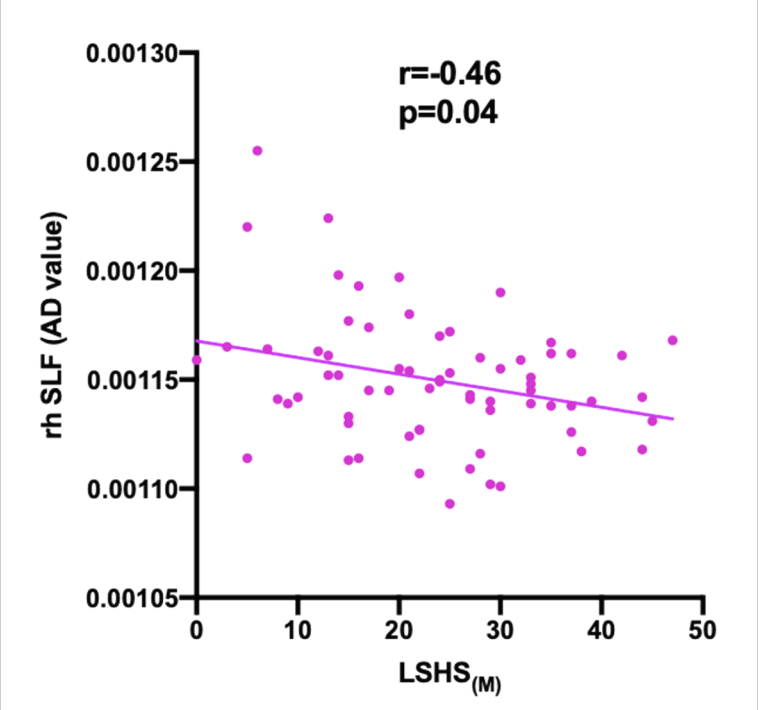

Figure 6. 9:AD correlation for $LSHS_{(M)}$ scores with rh SLF AD values.

6.4.5.2 AD Correlation with $LSHS_{(A)}$ Scores

A nonparametric test was performed between AD values and the $LSHS_{(A)}$. The results show significant negative correlation with SLF_RT ($P<0.05$), SLF_LT($P<0.05$), ILF_RT ($P<0.05$) and OL ($P<0.05$) (see Table 6.8).

Table 6. 7: Correlation of $LSHS_{(A)}$ scores with AD values

Correlation	SLF_rh	SLF_lh	ILF_rh	OL
Spearman r	-0.2406	-0.3232	-0.3217	-0.2613
p value	0.0481	0.0072	0.0075	0.0314

Key: ILF: inferior longitudinal fasciculus (lh), SLF: superior longitudinal fasciculus (rh & lh) and OL: occipital lobe.

6.4.5.3 AD Correlation with $LSHS_{(V)}$ Scores

A nonparametric test performed between AD values and visual scores of $LSHS_{(V)}$. The results showed no correlation.

6.7 Discussion

The principal aim of this chapter was to test whether alterations in diffusivity metrics, previously described in the literature, for patients suffering from hallucinations relative to patients without hallucinations and healthy controls, predict systematic shifts of DTI metrics with a measure of hallucination proneness in a large healthy sample of the population, consisting of 68 participants (28 males and 40 females). As described in the previous chapters, participants were asked to complete the $LSHS_{(M)}$ questionnaire and subjected to DTI imaging. FA, MD, RD and AD values were extracted and correlated with $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ scores.

The literature review showed that the majority of studies showed a relative reduction in FA and a relative increase in diffusivity measures (MD, RD and AD) in patients suffering from hallucinations relative to controls. The continuum model therefore predicts a negative correlation between $LSHS_{(M)}$ scores and FA measures and a positive correlation with diffusivity measures (MD, RD, AD) in the healthy population.

The correlation data presented here show significant negative correlations of $LSHS_{(M)}$ and $LSHS_{(A)}$ scores with MD, RD and AD (DTI) measures. $LSHS_{(V)}$ scores were not correlated with any DTI measures.

While FA differences between patients and controls, whether these are patients who do not suffer from hallucinations, or healthy controls, are commonly reported in the literature, this analysis does not show significant links between FA and any of the $LSHS_{(M)}$ scores in any of the selected regions.

The findings of this study contrast with previously published studies that investigated FA values in a sample of the schizophrenia population (Ashtari et al., 2007; Kyriakopoulos et al., 2009; Kyriakopoulos et al., 2008; Lee et al., 2009; Lee et al., 2013; Mulert et al., 2012; Rotarska-Jagiela et al., 2009; Tang et al., 2010). Interestingly, these reports are discrepant in terms of the direction of changes of FA values in schizophrenia patients, with some reporting increased FA (Mulert et al., 2012), and others reporting decreased FA in schizophrenia patients (Ashtari et al., 2007; Kyriakopoulos et al., 2009, 2008; Lee et al., 2013). Mulert et al. (2012) linked increased FA directly to AVH presentation, as these authors identified that there was a significant increase in FA values in patients presenting with AVH compared to those without, thereby indicating a direct link between FA values and the presentation of AVH symptoms in schizophrenic patients, rather than FA values being linked to all symptoms of schizophrenia. This finding is further supported by the findings of Ashtari et al. (2007). These authors identified a decrease in FA values in schizophrenia patients in the prefrontal regions, external capsule, pyramidal tract, occipitofrontal fasciculus, superior and inferior longitudinal fasciculi, and corpus callosum. However, they identified an increase in FA values in the arcuate fasciculus and this increase was directly correlated with the severity of auditory hallucinations (Ashtari et al., 2007). A recent study investigating the correlation between FA values and AVH

in the general population identified a positive correlation between FA values and AVH proneness in the right superior temporal gyrus (Spray et al., 2018). The findings of these studies suggest that alterations, whether increases or decreases, to FA are specifically associated with the development of AVH.

FA values are not specific to the type of changes (e.g., radial or axial) (Alexander, Lee, Lazar, & Field, 2007). Consistently, some studies have found no correlation with FA values, but they did find a correlation with MD, RD and AD (Liu et al., 2013). Therefore, this study conducted an analysis of MD, RD and AD and correlated these to $LSHS_{(M)}$ scores. In this chapter, a difference between the hallucination and control group in MD values in the STG white and grey matter was identified, specifically, a negative correlation between $LSHS_{(M)}$ score and MD values. This is in contrast to other previously published reports. Lee et al. (2009) reported increased MD in schizophrenia patients and identified a correlation between MD values in the left STG WM and auditory hallucinations, whereas Rigucci et al. (2016) identified no difference in MD values in schizophrenia patients compared to healthy controls. In agreement with that finding, Spray et al. (2018) reported no significant correlation between MD values and $LSHS_{(M)}$ scores in healthy individuals. Moreover, a negative correlation between RD values and $LSHS_{(M)}$ scores in the OL and a negative correlation between AD values and $LSHS_{(M)}$ scores in the IFL_RT, SLF_LT, SLF_RT and OL was identified in this study. The findings presented in this chapter are in apparent contrast to previous reports, with several studies reporting an increase in RD values in schizophrenia patients compared to healthy controls (Abdul-Rahman, Qiu & Sim, 2011; Levitt et al., 2012; Scheel, Prokscha, Bayerl, Gallinat & Montag, 2013; Seal et al., 2008; Zhang et al., 2018). Moreover, previous studies have reported an increase in AD between schizophrenia patients and healthy controls in several brain regions (Abdul-Rahman et al., 2011; Zhang et al., 2018). In contrast, Rigucci et al. (2016) found no difference in AD between patient and control groups .

In the sample tested in this study, there was a negative correlation between $LSHS_{(M)}$ scores and MD, AD and RD values. Moreover, using the $LSHS_{(A)}$ scores shows the same results as for the $LSHS_{(M)}$. However, the $LSHS_{(V)}$ scores did not show any correlation with areas related to visual or auditory areas.

6.7.1 Other Factors Linking Hallucinations to White Matter Microstructure

Kyriakopoulos and Frangou (2009) reviewed the literature linking DTI measures with early stage schizophrenia. Their main findings and conclusion are in line with previously reviewed work on chronic schizophrenia, namely the idea that wide ranging abnormalities in white matter tracts, which connect brain regions into functional networks, may explain the pathophysiology of hallucination caused by structural dysconnectivity. The review also systematically covers a range of explanations, many of them potential confounds in studies that compare patient groups with healthy controls.

6.7.1.1 Development

The regions identified with hallucinations in the literature (see Table 6.1) overlap significantly with white matter tracts that have independently been identified as tracts that undergo the most significant changes and may be related to ongoing motor and language development, namely the superior longitudinal fasciculus (SLF), the corticospinal tracts and the corpus callosum (Lebel et al., 2008). Other fibre tracts develop beyond the age of 30, such as the uncinate fasciculus and cingulum bundle, and therefore may be particularly sensitive to developmental disorders that may be caused by external factors such as brain injury or infection, premature birth, growth or nutrition problems, neglect (poor diet and health care), drug misuse during pregnancy, or child abuse, though a cause may also be genetically predetermined.

6.7.1.2 Genetics

Parnanzone et al. (2017) provide a literature review where they summarise the main DTI findings involving the different brain regions in patients affected at high-risk for psychosis. Their key finding is that in 16 out of 25 studies of participants at high risk of psychosis, FA reductions in a wide range of regions was reported, while three studies described increased and equal FA.

6.8 Conclusion

The key finding from this study is a negative correlation between $LSHS_{(M)}$ scores and MD, AD and RD values in a number of white matter tracts that have previously been identified to show increased diffusivity in schizophrenic patients compared to controls. No correlation between FA values and $LSHS_{(M)}$ scores was found.

The aim of the study was to test whether the continuum models of psychosis (Baumeister et al., 2017) can explain proneness to hallucinations in a healthy population. The FA data is inconclusive and FA is not correlated with $LSHS_{(M)}$ scores in any region. While the data does not support the continuum model as a potential explanation for hallucinations in a healthy population, it also provides no conclusive evidence that the model does not apply since non-significant, but overall negative, correlations might be considered to be consistent with the model.

The mean diffusivity data, on the other hand, is incompatible with explanations that rely on continuum models because the large population tested showed significant *negative* correlations between $LSHS_{(M)}$ indices and diffusivity measures in a number of fibre tracts.

While this finding is incompatible with our hypothesis and the model, it mirrors the results reported in the two previous chapters: the more hallucination prone participants in this study appear not only to have increased brain volumes (Chapter 4) and functional activation (Chapter 5) in areas where hallucinating patients would exhibit the opposite pattern, they also show relative decreases in mean diffusivity in major fibre tracts.

In the patient data reviewed in the introduction, decreases in FA and increases in MD, RD or AD are often represented as signs of pathology. This representation is a reasonable shorthand in the application of DTI to, for example, neurodegenerative diseases such as multiple sclerosis (Sbardella et al., 2013), where the effects of demyelination directly predict the observed changes. Pathology may offer a plausible explanation for hallucinations, where specific differences between patient groups and controls are seen, but it is important to bear in mind that, as shown for example by Knöchel et al., (2012), microstructural aberrations in

schizophrenic patients may have a genetic component since patient's relatives showed similar alterations at a lower magnitude compared to controls. Sommer et al., (2010) further showed that higher Schizotypal Personality Questionnaire scores, lower education, and higher family loading for psychiatric disorders, but not the presence of AVH, were associated with lower global functioning, which may be an indication of brain pathology or developmental disorders.

These considerations, together with the findings in this and the three previous chapters, would support the conclusion that the microstructural features described for the patient population are hallmarks of psychosis, but not of proneness to hallucinations (Diederen et al., 2012, functional lateralisation data).

The model would, however, predict at least one common variable, linked to hallucination proneness, to be shared across the healthy and patient population. Our data provides no evidence that microstructural structural brain parameters provide this measure.

As in the previous chapters, where equally counterintuitive data was shown, it is striking that all participants were highly functioning individuals – most of them were university students – yet a significant proportion reported high levels of hallucination proneness and these individuals had lower mean diffusivity measures in major fibre tracts than their colleagues who very rarely experienced hallucinations, if ever. If increased diffusivity is an indicator of the likelihood of psychosis, rather than the cause for hallucinations, then an interesting question is whether the relative reduced diffusivity, and with it perhaps the ability to process information better may, instead of preventing hallucinations, actually enable sufferers of hallucinations to cope with the experience better. This post-hoc explanation would explain that a high proneness to hallucination is linked to higher brain volumes (Chapter 4), increased functional activation (Chapter 5) and reduced diffusivity (this chapter) in a healthy population.

Chapter 7

Links Between Arcuate Fasciculus Tractography Measures and Hallucination proneness

7.1 Introduction

The neurobiology underlying auditory verbal hallucinations (AVH), as one of the key symptoms for schizophrenia, are poorly understood. Uncovering the pathophysiological basis might provide insights into alternative therapeutic methods for the 25% of patients who do not respond to existing antipsychotic medication (Shergill et al., 1998).

Recent findings in functional magnetic resonance imaging (fMRI) have revealed significant aspects of the AVH neurobiology.

Jardri et al. (2011) demonstrated consistent activation during AVH in several brain areas, for example the right and left temporal-parietal cortex and Broca's area and its right-sided homologue (Diederen et al., 2010). Temporo-parietal activation during AVH is linked with the perception of voices, while activity in bilateral inferior frontal areas indicates language production. Words created in these areas can be experienced as AVH. Ford et al. (2007) noted that the corollary discharge mechanism was malfunction: a neuronal circuit which inhibit the sensory outcomes of self- generated actions. Inadequate corollary discharge into the speech system might arise from disturbed communication between frontal and temporal regions (Whitford et al., 2010). This disrupted connectivity may arise from microstructural abnormalities on the arcuate fasciculi, the fibre tract between Broca area and the Wernicke area (De Weijer et al., 2011).

White matter fascicles (WM) are the main constituent of the brain connectome (Mandonnet et al., 2018) and can be visualised and analysed using diffusion tensor imaging (DTI). One such major tract that connects cortical language areas is the Arcuate Fasciculus (AF) (Fletcher et al., 2010). Variation in the connectivity between the frontal and temporal hemisphere language areas, connected by the AF, has been linked to auditory verbal hallucinations (AVH) (Ford et al., 2007; McCarthy-Jones et al., 2015; Whitford et al., 2012). It has been

demonstrated that abnormalities in the functional connectivity of the AF are due to differences in the microstructure of the WM (Takahashi, Sakurai, Davis, & Buxbaum, 2011). Despite the suggestion that asymmetric anomalies provide a potential explanation for clinical features, few studies investigated white matter asymmetries along the Arcuate Fasciculus (AF) and other associative white matter fibres (Rossi et al., 1994; Bleich-Cohen et al., 2009). In a recent study, left lateralization of the reconstructed direct pathway AF rationale was found in more than 80% of healthy subjects, while the remaining subjects had reasonably symmetrical AF representation (Catani et al., 2007). AF asymmetry was correlated with improved verbal memory of newly learned words, although AF asymmetry did not offer any benefit in that research. A further pilot study identified left asymmetry of AF among 18 right-handed with left > right fractional anisotropy (FA) (Rodrigo et al., 2007). Result left asymmetry of the AF was also observed, irrespective of hand or functional language lateralization, in 20 healthy subjects, with functional and structural asymmetries correlating to the right but not to the left (Vernooij et al., 2007). Therefore, while some evidence has been found in these studies, the impact of handiness on the structural asymmetry of the AF and relationship between structural asymmetry and basic language functions remains unclear.

Table 7. 1: Previous studies investigated the Arcuate Fasciculus (AF). (↑) increase, (↓) decrease. (N/A) not available.

Authors	**Sample**	**Results**	
		LT AF	**RT AF**
Burns et al., 2003	30 patients 30 healthy	↓ FA in patients	FA no differences
Hubl et al., 2004	13 patients 13 healthy	↑ FA in patients	↑ FA in patients
Shergill et al., 2007	33 patients 40 healthy	↑ FA in patients	↑ FA in patients
Knöchelet al., 2012	28 patients 22 Healthy	↑ FA in patients	N/A

Kubicki et al., 2005	21 patients 26 healthy	↓ FA in patients	N/A
Munoz Maniega et al., 2008	31 patients 51 healthy	↓ FA in patients	FA no differences
Phillips et al., 2009	23 patients 22 healthy	↓ FA in patients ↓tract volume in patients	FA no differences Volume no differences
Catani et al., 2011	17 AVH patients 11 Non-AVH patients	↓ FA in patients MD no differences	↓ FA in patients MD no differences
De Weijer et al., 2011	44 patients 42 healthy	↓ FA in patients ↑ RD in patients MD and AD no differences	↓ FA in patients ↑ RD in patients
Falkenberg et al.,2019	66 patients 76 healthy	AF tract longer in patients	AF tract longer in patients
Ćurčić-Blake et al., 2015	17 patients	↓ FA in patients	N/A
Dooley et al., 2019	100 patients 25 healthy	↓ RD in patients FA no differences	↓ RD in patients FA no differences

Key: FA: fractional anisotropy, MD: mean diffusivity, AD: axial diffusivity, AF: arcuate fasciculus, LT: left, RT: right, ↑: increase, ↓: decrease, AVH: auditory verbal hallucination and Non-AVH: non auditory verbal hallucination.

The abnormalities in the brain connectome that result in AVH remain incompletely understood (Allen et al., 2012). Many studies have investigated fibre tract connectivity in relation to AVH (Table 7.1). Some studies reporting abnormalities to the bundles which connect the temporal to frontal regions (Psomiades et al., 2016) and others identifying abnormalities in the AF being related to AVH (Abdul-Rahman et al., 2012; Geoffroy et al., 2014; Hubl et al., 2004; Society, 2011). Fractional Anisotropy (FA) is one of the measures that can be extracted from DTI and reflects the WM fibre organisation and is most frequently used to measure anisotropic diffusion (Beaulieu, 2002b). Previous studies have reported decreased

FA in the AF in schizophrenia patients presenting with AVH compared to non-AVH schizophrenia patients (Geoffroy et al., 2014; Minami et al., 2003; Phillips et al., 2009; Ćurčić-Blake et al., 2015; De Weijer et al., 2011; Muñoz Maniega et al., 2008). In contrast, one three studies reported an increased FA in the AF in schizophrenia patients with AVH compared to those without (Hubl et al., 2004; Shergill et al., 2007; Knöchel et al., 2012). Most studies have focused on global WM integrity of the AF to differentiate between AVH and non-AVH patients. Alteration or variation in the (FA, MD, AD and RD) are also perceived as changes or differences in the "integrity" of the microstructure of the white matter (or, in contrast, structure damage, deterioration or degeneration). This indicates that some part of the white matter microstructure is damaged (Jones et at., 2013). Differences in the integrity of AF in relation to AVH in the left and right lobe remain unclear (Psomiades et al., 2016). Whereas, some studies report a reduction in FA in the right AF (Catani et al., 2011), others have identified a positive relation between FA and AVH severity (Ćurčić-Blake et al., 2015). Some studies have correlated scores on a hallucination questionnaire and the AF, and reported a positive correlation between the scores and the tract length in both sides of AF, this result showed significant longer tracts along the AF in patients with AVH, as well as a major overall length asymmetry with longer AF on the left side (Falkenberg et al., 2019). Another study reported decreased FA and an increase in the mean diffusivity (MD) in the left AF of patients with AVH compared to non-AVH patients (Mandl et al., 2013). However, (Dooley et al., 2019) reported a reduction in radial diffusivity (RD) in patients with AVH compared to those without in both the right and left AF. However, in that study no difference in FA between the groups reported.

Continuum Hypothesis

Baumeister et al. (2017) proposes three models that each leads to a distinct set of testable hypotheses that are schematically represented below Figure 7.1. For more details about the hypothesis please to refer to chapter 4.

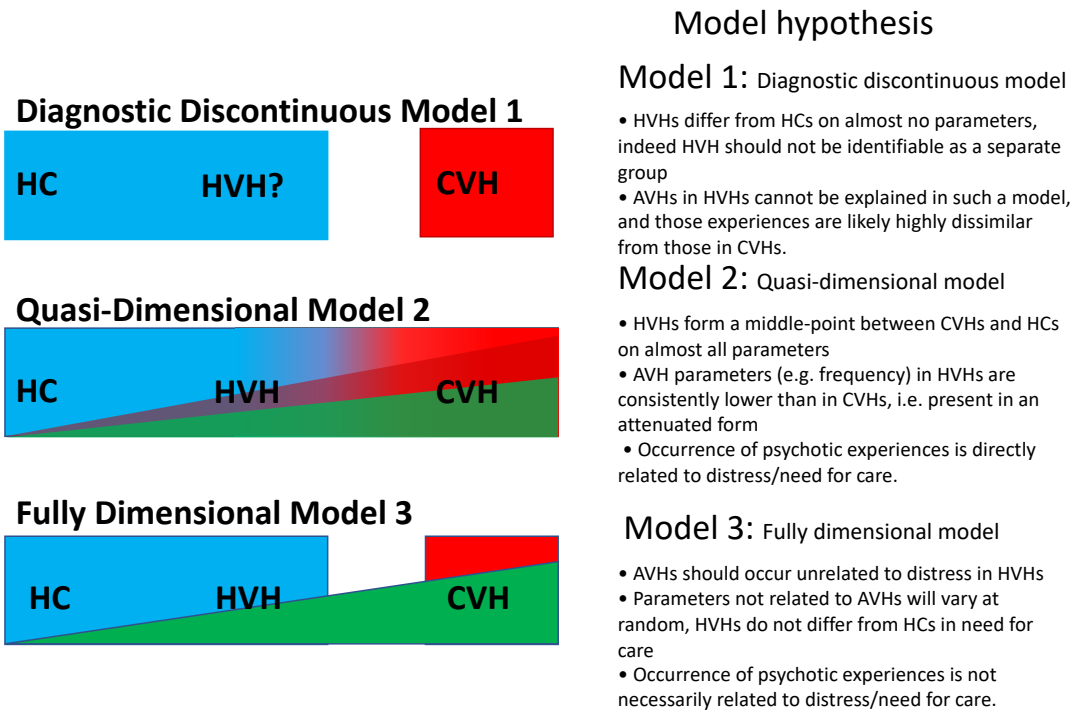

Figure 7.1: Schematic diagram of the three models reproduced from Baumeister et al. (2017).

In this chapter, I will investigate the AF in both the left and right lobe to identify potential differences in the integrity of the microstructure of WM in relation to severity of AVH in a healthy population. AVH severity will be assessed using the Launay-Slade Hallucination Scale modified $LSHS_{(M)}$ (Morrison's et al., 2000), and participants will be recruited via email at the University of Liverpool.

I hypothesise that the correlation of $LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$ scores with FA and tract volume will be negative, and the correlation with MD, AD, RD and tract length will be positive to reflect data reported in patients. Also, I predict that the lateralization index of the (FA, tract volume and tract length) will positively correlated with the hallucination scores ($LSHS_{(M)}$), which mean left lateralization (more to the left than the right).

7.2 Methodology

7.2.1 Participants

69 participants out of 75 underwent to participate in the MRI scan. The neuroradiologist reported an abnormal finding in one of the 69 participants and that participant was excluded

from subsequent analyses. So, the total number of participants was 68 (25 males and 43 females), with an average age of 29.1 years (SD =11.956, range19-66).

7.2.2 Parameters

The same parameters as mentioned in chapter 6 were used to perform the DTI sequence and this sequence was used to perform the tractography analysis.

7.2.3 Image Software Analysis

ExploreDTI v4.8.6 was used to analyse the DTI sequence (http://www.exploredti.com), which is a graphical toolbox to investigative fibre pathways and diffusion tensor image. A key advantage of tractography packages, such as ExploreDTI is that they provide explicit structural measures, such as tract length and volume, which are not available from the voxel based analysis used in chapter 6.

7.2.4. Image Preprocessing

The first step of image preprocessing included converting the image from Dicom to Nifti. Secondly, the text file was converted to include the gradient direction and the b-value to B-matrix. Images were reordered according to the MRI machine's output. Then, the data was flipped and permuted employing ExploreDTI. Subsequently, the data was corrected for signal drifting across the different dMRI volumes by estimating the change in signal (Vos et al., 2017). Then, the non-DW image volumes were reordered with respect to the b-value used in the sequence, the Gibbs ringing correction was applied to remove the Gibbs ringing artefacts (Perrone et al., 2015). Finally, the images were corrected for motion and distortion (Leemans & Jones, 2009) using the T1 sequence data as a reference.

7.3. Data Analysis

Whole brain tractography performed by ExploreDTI for all the participants is illustrated in Figure 7.2. The whole brain tracts were created using all voxels in the image with the default ExplorDTI default parameters: FA threshold = 0.2, and an angle threshold = 30°.

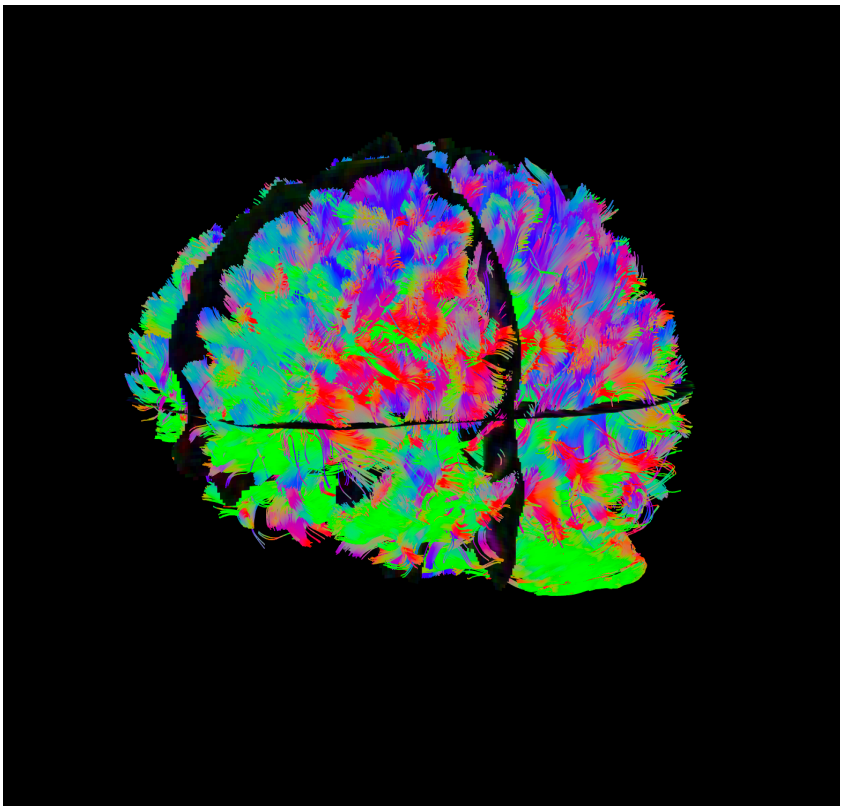

Figure 7.2: Whole brain tractography after calculating whole tracts in the brain for one of the participants in this study. This image shows all fibre tracts in the different directions. Tractography with FA threshold 0.2 and an angle threshold of 30^{o}.

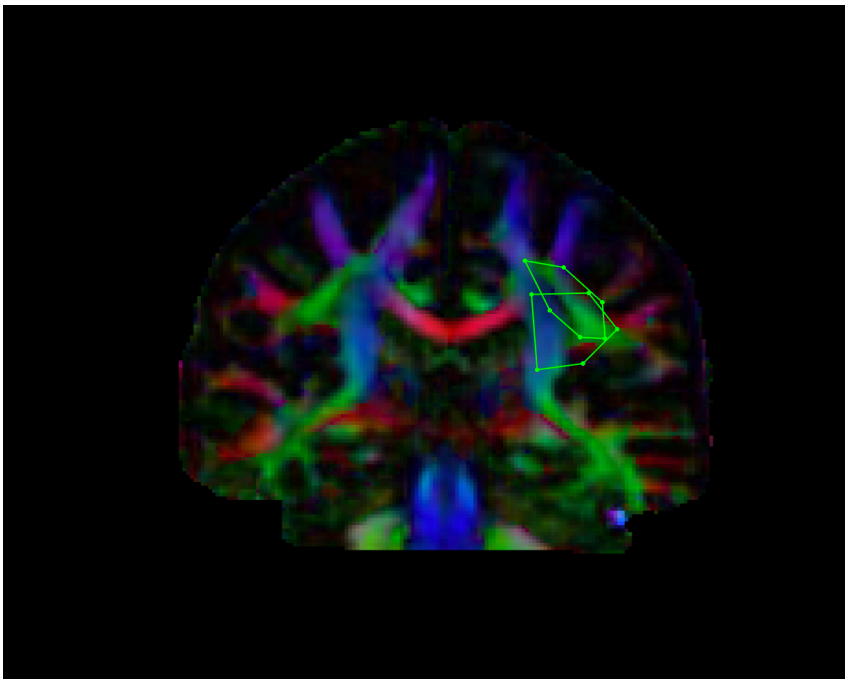

Figure 7.3: Illustration of drawing region of interests on the lh AF.

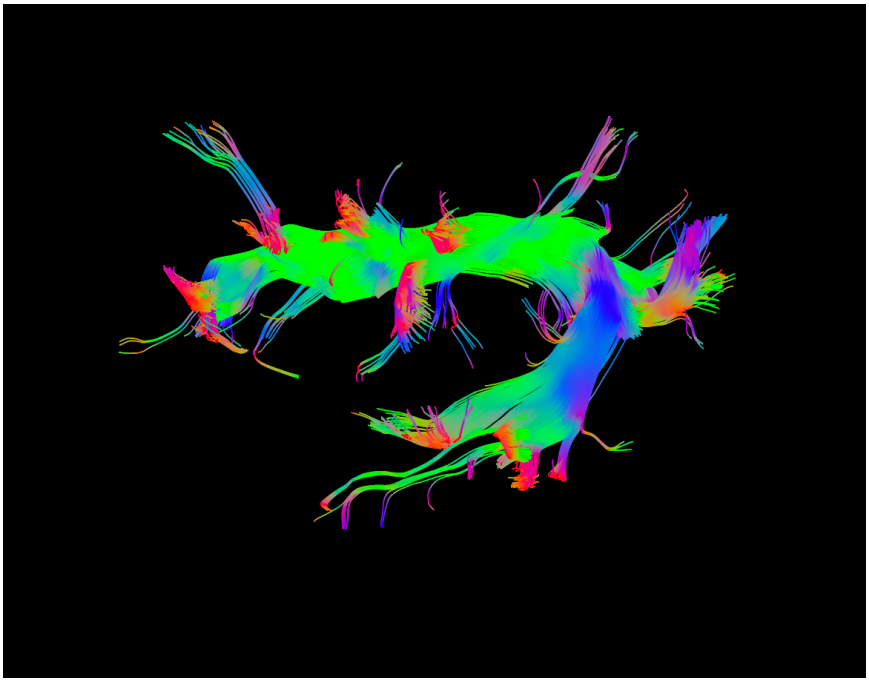

Figure 7.4: Illustration of the lh AF extracted as drawn in Figure 5.2.

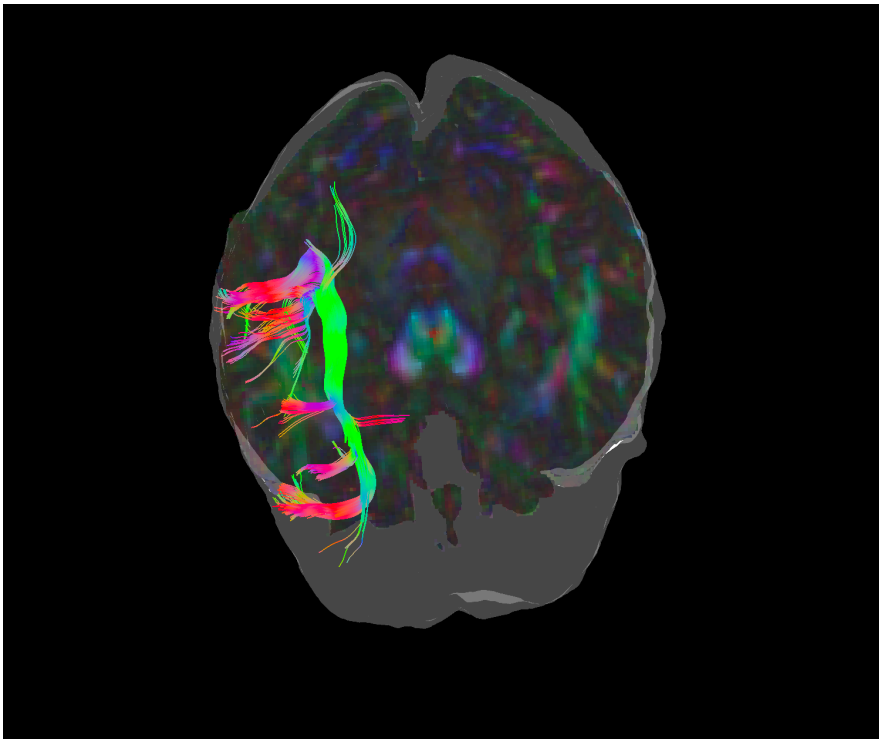

Figure 7.5: Rh AF extracted from whole tract brain through axial cut.

Two regions of interest, manually drawn in the coronal plane, to extract the left AF are illustrated in Figure 7.3. Those two regions will allow the extraction of all tracts penetrating

them. Illustrated in Figure 7.4 is the AF extracted and excluded from other tracts. Similar steps were used to extract the right AF, illustrated in Figure 7.5. Employing ExploreDTI, the left (LT) and right (RT) AF were set as regions of interest to allow the extraction of the LT and RT AF from all participants, by enabling the AF to be reliably identified in native space through warping images of different sizes and geometries to a common template. After all tracts were extracted, ExploreDTI extracted the metrics (FA, MD, AD, RD, tract length and tract volume) for the two fibre tracts for each participant individually.

All statistical analyses were performed employing GraphPad Prism Version 8.3.0. A normality test was carried out on all data to analyse whether they were normally distributed. A nonparametric Spearmen r correlation test was performed between the values extracted from left arcuate fasciculus and the ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$). Furthermore, a nonparametric spearmen r correlation test was performed on the values extracted from the right AF with $LSHS_{(M)}$ scores, $LSHS_{(A)}$ scores and $LSHS_{(V)}$ scores.

Asymmetry (Lateralization Index (LI))

We computed lateralization index (LI) according to $2(M_{left} - M_{right})/(M_{left}+M_{right})$, where M denote FA to study the AF asymmetry (Luders et al., 2004). The more positive the index, the greater left anisotropy or diffusivity compared to the right hand (left asymmetry), while the more negative index is the greater anisotropy or diffusivity to the left side (right asymmetry).

As in the previous chapters, the hypothesis that is tested is that systematic differences observed in AF metrics between patients experiencing hallucinations and healthy controls predict the correlation between FA metrics (FA, MD, RD, AD, tract volume and tract length) and hallucination scales scores ($LSHS_{(M),}$ $LSHS_{(A)\ and}$ $LSHS_{(V)}$) in the healthy population. In addition, lateralization index computed for the FA and correlated with the hallucination scales and the results predicted to be a positive correlation.

7.4 Results

7.4.1 Correlation of LT & RT Arcuate Fasciculus measures with $LSHS_{(M)}$ Scores.

A nonparametric correlation test was performed between left and right AF indices (FA, MD, AD, RD, tract length and tract volume) and $LSHS_{(M)}$ scores. The data extracted from the left AF tract showed a significant negative correlation with $LSHS_{(M)}$ scores for the AD metric, $p< 0.0250$ (Table 7.2), and MD, $p< 0.0399$ (Table 7.2), Figure 7.6 and 7.7. The correlation between the $LSHS_{(M)}$ scores and the AD in the right AF showed a trend towards significance, $p< 0.0571$ (Table 7.3). Moreover, a positive correlation notice between FA value bilateral with $LSHS_{(M)}$, however, it does not reach to a significant. No other significant correlations were observed. No significant correlation test was shown between the tract length and tract volume with $LSHS_{(M)}$ scores.

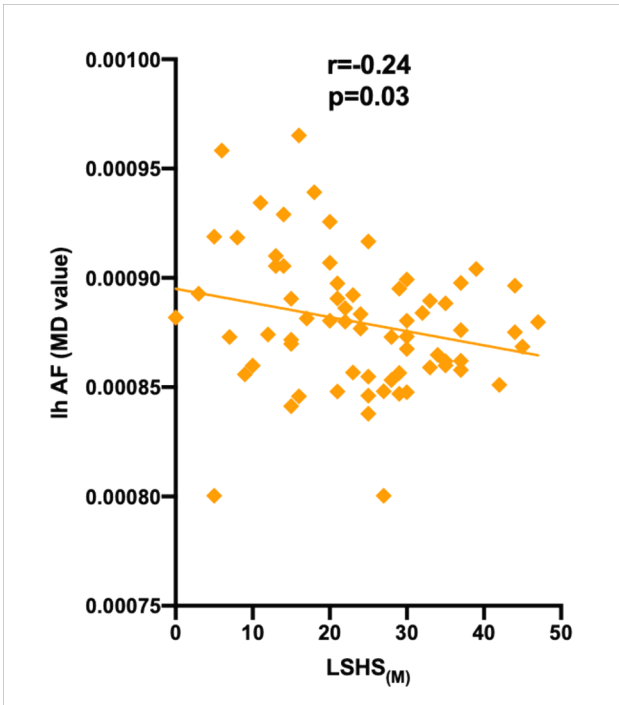

Figure 7.6: Correlation of MD value with $LSHS_{(M)}$ in the lh AF.

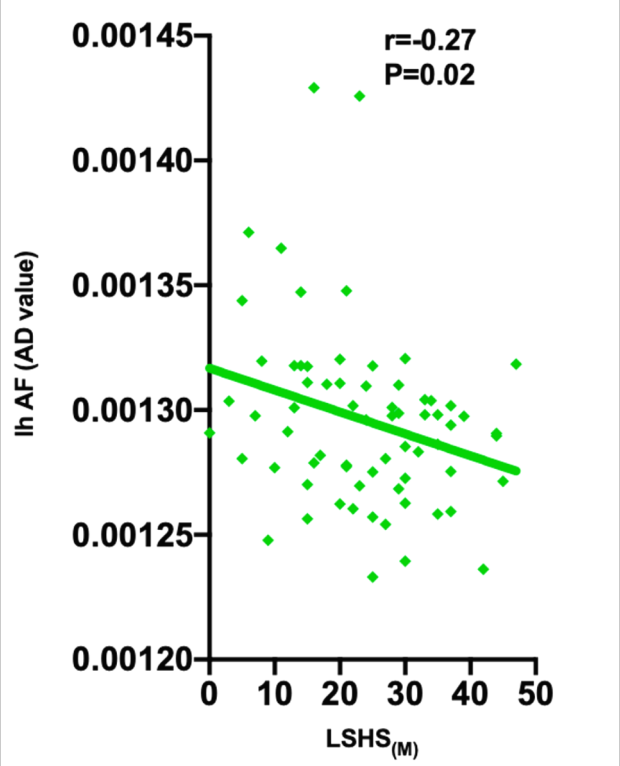

Figure 7.7: Correlation of AD value with $LSHS_{(M)}$ in the lh AF.

Table 7.2: Nonparametric test for the left hemisphere (lh) of the Arcuate Fasciculus (AF) values with $LSHS_{(M)}$ scores.

Correlation	FA (LT AF)	MD (LT AF)	AD (LT AF)	RD (LT AF)	Tract Volume (LT AF)	Tract Length (LT AF)
Spearman r	0.09223	-0.2499	-0.2717	-0.2163	0.01561	-0.02671
p value	0.4544	0.0399	0.0250	0.0764	0.8994	0.8288

Key: FA: fractional anisotropy, MD: mean diffusivity, AD: axial diffusivity, RD: radial diffusivity, AF: arcuate fasciculus and LT: left.

Table 7. 3:Nonparametric test for the right hemisphere (rh) of the Arcuate Fasciculus (AF) values with $LSHS_{(M)}$ scores

Correlation	FA (RT AF)	MD (RT AF)	AD (RT AF)	RD (RT AF)	Tract Volume (RT AF)	Tract Length (RT AF)
Spearman r	0.06428	-0.1812	-0.2318	-0.1166	-0.06327	-0.1322
p value	0.6025	0.1391	0.0571	0.3437	0.6082	0.2826

Key: FA: fractional anisotropy, MD: mean diffusivity, AD: axial diffusivity, RD: radial diffusivity, AF: arcuate fasciculus and RT: right.

7.4.2 LT & RT (AF) Indices Correlation with $LSHS_{(A)}$ Scores

A nonparametric correlation test was performed between LT & RT AF and the $LSHS_{(A)}$ scores. Table 7.4 reports the nonparametric correlation test performed between LT AF indices and the $LSHS_{(A)}$ scores, which showed no significant correlation. However, the data identified a significant negative correlation with the $LSHS_{(A)}$ scores in the right AF with mean AD values, $p< 0.0340$ in (Table 7.5) shows the correlation between the $LSHS_{(A)}$ scores and the mean values of the RT AD in the AF.

Table 7.4: Nonparametric test for lh Arcuate Fasciculus values with $LSHS_{(A)}$ scores.

Correlation	FA (LT AF)	MD (LT AF)	AD (LT AF)	RD (LT AF)	Tract Volume (LT AF)	Tract Length (LT AF)
Spearman r	0.06039	-0.1391	-0.1630	-0.1555	0.16	0.0.6
p value	0.6247	0.2578	0.1842	0.2053	0.18	0.59

Key: FA: fractional anisotropy, MD: mean diffusivity, AD: axial diffusivity, RD: radial diffusivity, AF: arcuate fasciculus and LT: left.

Table 7. 5: Nonparametric test for rh Arcuate Fasciculus values with $LSHS_{(A)}$ scores

Correlation	FA (RT AF)	MD (RT AF)	AD (RT AF)	RD (RT AF)	Tract Volume (RT AF)	Tract Length (RT AF)
Spearman r	0.04730	-0.1695	-0.2575	-0.1240	0.07	-0.76
p value	0.7017	0.1670	0.0340	0.3137	0.56	0.54

Key: FA: fractional anisotropy, MD: mean diffusivity, AD: axial diffusivity, RD: radial diffusivity, AF: arcuate fasciculus and RT: right.

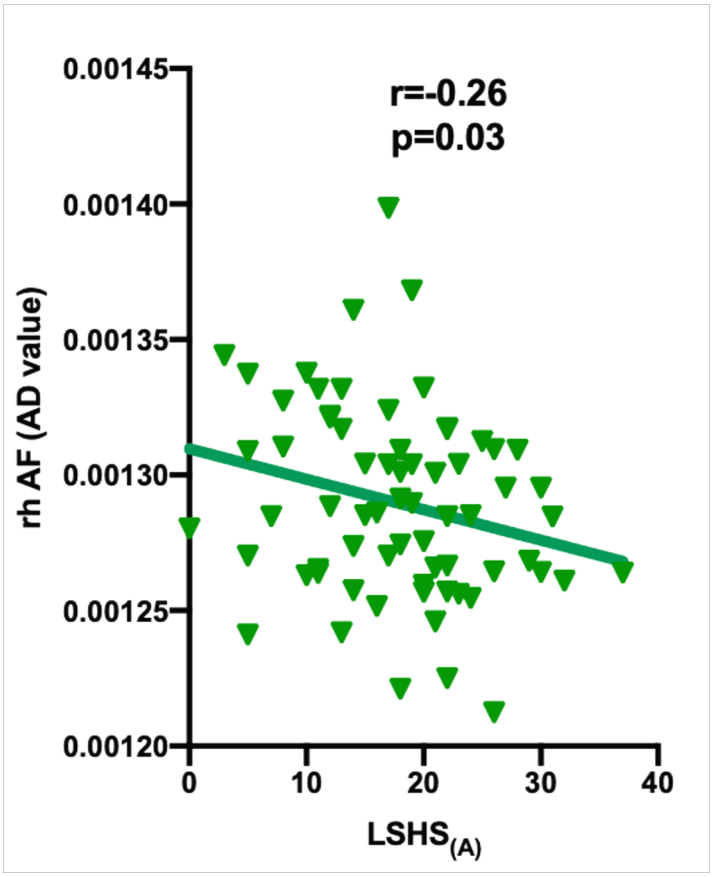

Figure 7.8: Correlation of the rh AD value with $LSHS_{(A)}$ scores.

7.4.3 LT & RT (AF) Indices Correlation with $LSHS_{(V)}$ Scores

A nonparametric test was performed between the left AF indices and the $LSHS_{(V)}$ scores (Table 7.6). The result showed a strong trend toward a significant negative correlation with subscale of the visual scores and the left AD mean values, $p< 0.0596$. Moreover, the results showed a moderate trend towards a significant negative correlation with the visual subscale scores and left MD mean values, $p< 0.0672$ (Table 7.6). A nonparametric test was performed between the right AF indices and subscale of visual scores (Table 7.7). The results identified no significant correlation between visual subscale scores and right AF indices.

Table 7.6: Nonparametric test for lh Arcuate Fasciculus values with $LSHS_{(V)}$ scores.

Correlation	FA (LT AF)	MD (LT AF)	AD (LT AF)	RD (LT AF)	Tract Volume (LT AF)	Tract Length (LT AF)
Spearman r	0.08395	-0.2233	-0.2296	-0.1831	-0.08	-0.09
p value	0.4961	0.0672	0.0596	0.1351	0.5	0.44

Key: FA: fractional anisotropy, MD: mean diffusivity, AD: axial diffusivity, RD: radial diffusivity, AF: arcuate fasciculus and LT: left.

Table 7.7: Nonparametric test for rh Arcuate Fasciculus values with the $LSHS_{(V)}$ scores.

Correlation	FA (RT AF)	MD (RT AF)	AD (RT AF)	RD (RT AF)	Tract Volume (RT AF)	Tract Length (RT AF)
Spearman r	0.05577	-0.1204	-0.1149	-0.07493	-0.15	-0.11
p value	0.6515	0.3280	0.3510	0.5437	0.21	0.34

Key: FA: fractional anisotropy, MD: mean diffusivity, AD: axial diffusivity, RD: radial diffusivity, AF: arcuate fasciculus and RT: right.

7.4.4 Lateralization Index (LI) FA

To test whether the reported differences in lateralisation that have been described for patients compared to controls translate into the healthy population, lateralisation indices were computed for the measures obtained with ExploreDTI and correlated the $LSHS_{(M)}$ scores. Table 7.8 shows no significant correlation between LI FA, LI tract volume and LI tract length with $LSHS_{(M)}$. The correlation was not significant ($r=0.16$, $p<0.17$), Figure 7.9. However, the correlation value above zero for FA, tract volume and tract length, which mean left lateralization of the three measurements.

Table 7.8: Nonparametric test for the Lateralization index of FA, tract volume and tract length correlated with LSHS$_{(M)}$.

	LI FA	LI tract volume	LI tact length
Spearman r	0.16	0.07	0.2
P value	0.17	0.53	0.38

Key: LI: lateralization index, FA: fractional anisotropy.

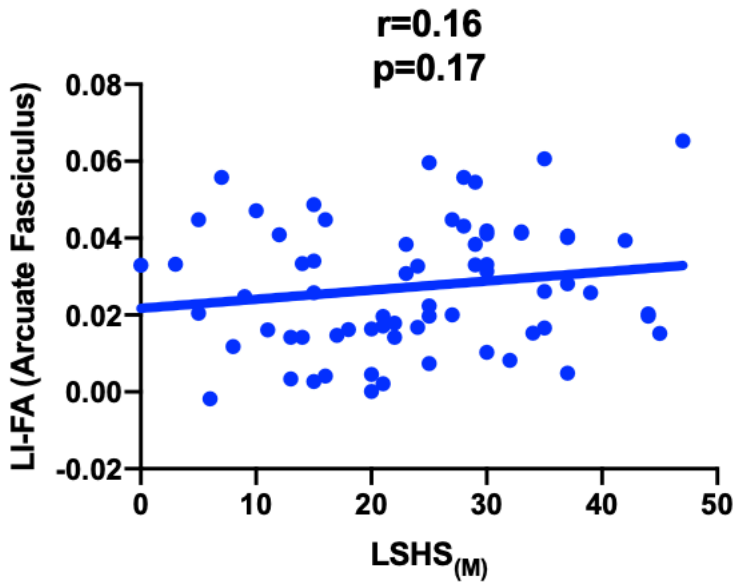

Figure 7.9: Scatter plot shows a positive correlation between LI FA arcuate fasciculus and LSHS$_{(M)}$ scores.

7.5 Discussion

In this chapter, I set out to identify the LSHS$_{(M)}$, LSHS$_{(A)}$ and LSHS$_{(V)}$ scores correlation with AF indices for both sides. To do so, I recruited a total of 68 participants (28 males and 40 females). Participants were asked to complete the LSHS$_{(M)}$ questionnaire and subjected to DTI sequence. FA, MD, RD, AD values, tract volume and tract length for both sides of AF were extracted and correlated with LSHS$_{(M)}$ scores. This study reports a significant reduction with MD and AD in left Arcuate fasciculus. Moreover LSHS $_{(M)}$ was closely correlated significantly with AD values in right AF. Finally, a greater Left lateralization of (FA, tract volume and tract length) in the AF, positively correlated with LSHS$_{(M)}$ scores.

The indices extracted from the AF and correlated with $LSHS_{(M)}$ scores. FA values in the RT and LT AF correlated with $LSHS_{(M)}$ scores and showed no correlation. Interestingly, previous reports are discrepant in terms of the direction of changes of FA values reported with some reporting a decrease in FA (Abdul-Rahman et al., 2012; Catani et al., 2011; Ćurčić-Blake et al., 2015; De Weijer et al., 2011; Knöchel et al., 2012; McCarthy-Jones et al., 2015), and others reporting an increase in the FA (Hubl et al., 2004). Many of these studies did not use LSHS to correlate FA values and the presentation of AVH. However, three studies used the psychometric of Positive and Negative Syndrome Scale (PANSS) (Peralta & Cuesta, 1994), which is used as a Schizophrenia diagnostic. The result of these studies were conflicting, with some reporting a positive correlation between FA values and PANSS (Abdul-Rahman et al., 2012; De Weijer et al., 2011; Seok et al., 2007) and others a negative correlation between PANSS and FA values (Boos et al., 2013; Ćurčić-Blake et al., 2015).

In this study, MD and AD values in the left AF negatively correlated with $LSHS_{(M)}$ scores, while AD values in the RT AF demonstrated a marginal negative correlation with $LSHS_{(M)}$ scores. A recent study reported a similar correlation as reported in this study (Dooley et al., 2019). However, previous studies have reported increases in the RD in the patients compared to control participants, which contrasts with the findings reported in this study (De Weijer et al., 2011; Fletcher et al., 2010; McCarthy-Jones et al., 2015). However, other studies have reported no differences in RD of patients compared to control participants, in line with results in this study (Abdul-Rahman et al., 2012; Catani et al., 2011).

The results in this study reported significant a negative correlation in MD and AD values with $LSHS_{(M)}$ in the LT AF, reflecting differences int the connections, most probably due to the orientation or number of axons, or differences in the integrity of the axonal or myelin sheath (Beaulieu, 2002a). Interestingly, the differences in the mean indices of the AF values between groups was strongest in the left AF and this is in contrast with many previous reports (Abdul-Rahman et al., 2012; Chawla, Deep, Khandelwal, & Garg, 2019; Dooley et al., 2019). Through the result of the lateralization index, which shows FA value more in the left side than the right side. Most of the previous research has focused on patients with auditory hallucinations, whereas in this study, I recruited healthy participants. Consistently, a recently published study recruited both schizophrenia patients with AVH and a non-clinical population that presents with AVH to investigate whether the WM alterations underlying AVH are different in the two

populations (Di Biase et al., 2020). These authors found that WM pathology associated with AVH was independent of diagnostic status (Di Biase et al., 2020).

The greater leftward lateralization correlation of (FA, tract volume and tract length) in the left Arcuate Fasciculus (AF) with hallucination severity scales may be explained relative deficiency in the bundle with right Arcuate Fasciculus compared to the left in the high hallucination proneness. Thus, the discrepancy between the white matter consistency of the left Arcuate Fasciculus and the accentuation of the normal left larger than the right Arcuate Fasciculus indicates an aberrant fronto-temporal connectivity. The hyperconnectivity between frontal and temporal brain regions can affect corollary discharge of neural signals from frontal speech areas to auditory cortex (Abdul-Rahman et al., 2012). Moreover, this abnormal connectivity between the frontal and temporal lobe lead to facilitate functional imbalance between language production and language perception areas (Rotarska-Jagiel et al., 2009). In addition, disrupted frontal - temporal connectivity may lead to a dysfunctional language network, which may, in turn, be responsible for auditory hallucination (Hubl et al., 2004). Through inner speech, these changes can contribute to irregular coactivation in regions associated with the auditory treatment of external stimuli, which may account for inability of patients to differentiate between self-generated thoughts and external stimulus (Chawla et al., 2019). Also, increased FA in Arcuate Fasciculus may lead to hypercoupling of activity in speech perception which may play a part in the production of auditory hallucination (Whitford et al., 2012).

Previous studies comparing patients with controls report greater FA in the in the left arcuate fasciculus than the right and that is was positively correlated with $LSHS_{(M)}$, which explained a relative deficiency in the number of axonal bundled within the right AF compare the right AF (Hyatt & Yost, 1998). This results in line with previous studies found increased left FA of the AF on in the patients with auditory hallucination compared to control (Shergill et al., 2007; Knöchelet al., 2012). Thus, the distinction between the white matter integrity of the left arcuate fasciculus and the accentuation of the normal left greater than the right asymmetry of the FA in the arcuate fasciculus indicates an aberrant fronto-temporal connectivity (Heinks-Maldonado et al., 2007; Startup et al., 2008).

This study noticed a significant negative correlation between $LSHS_{(M)}$ scores and MD, and AD values in the left arcuate fasciculus. However, these results do not support the continuum

theory. The results in this study are distinct from those of prior MRI structural studies. Such a variation could be related to the characteristics of the samples. Most previously published papers have employed a smaller sample size than reported in this study and therefore discrepancies in results may arise.

In this study the MD and AD negatively correlated to the $LSHS_{(M)}$ scores, which may mean thicker myelination. A possible explanation for this result is that ligodendrocytes, cells responsible for the myelination of axons, increased (Rios et al., 2003). As oligodendrocytes mature their processes build a myelin sheath which repeatedly envelops and then compacts a segment of the axon (Kipp et al., 2012). The process occurs across the axon diameter and frequently remyelinated along the axon reduces the axon diameter (AD) [this needs a reference]. Voluntary exercise, for example running, has been linked to increased oligodendrocyte maturation (Krityakiarana et al., 2010). It is therefore possible that reductions in the FA and increases of MD and AD values, which have been reported for psychotic patients, are directly linked to behavioural differences, for example the engagement in sports.

Social enrichment (Juraska and Kopcik, 1988) has also been linked to increases in myelination. The brain structure hypermyelination or oligodendrocytes generate further during more socialise (Makinodan et al., 2012). Which mean the people scores high in the $LSHS_{(M)}$ were more socialise and leaded to increase the myelination axons.

The result of this chapter is consistent with the other results in chapters 4, 5 ,6. All results were surprisingly showing the opposite finding to the literature.

7.6 Conclusion

In this study, I identified a significant negative correlation between the $LSHS_{(M)}$ scores and MD and AD values in the left AF, and a marginal negative correlation with AD in the right AF. Moreover, a positive correlation between FA values and $LSHS_{(M)}$ scores on both sides of the AF were identified. Moreover, there were differences between the low and high hallucination proneness in the left AF in the mean MD, AD. These results indicate that the participants with lower diffusivity hallucinate more than participants with higher diffusivity.

These data show the opposite pattern of what patient studies, which mostly show a reduction in FA and increase in diffusivity measures when comparing patients with controls. The data therefore do not provide evidence that supports the continuum model (Baumeister et al., 2017).

Chapter 8

General Discussion

The discovery that healthy individuals experience hallucinations without the need for treatment and do not seem to endure the substantial distress that hallucinations cause in psychiatric populations has led to a significant interest and a proposal for continuum psychosis models (Baumeister et al., 2017). This study tests the continuum theory, which predicts that neural markers differentiating psychotic patient populations from healthy controls also systematically covary with hallucination proneness in the healthy population. Measures of hallucination proneness in the healthy population were correlated with structural (volumetric), functional (fMRI activation for a range of tasks) and microstructural (voxel based DTI and tractography) neuroimaging data.

The Launay-Slade Hallucination Scale (LSHS, Bentall & Slade, 1985) is ideally suited for the research reported here, because of its brevity, acceptability to healthy samples, its validity, as attested by its known correlates with psychosis related variables, and its previous use in imaging studies. The Launay-Slade Hallucination Scale, modified by Morrison et al. (2000), $LSHS_{(M)}$, was used to measure the tendency to report subclinical hallucinatory-like experience. An exploratory factor analysis was conducted using principal components analysis to extract subscales that measure auditory and visual hallucination. Furthermore, the Persecution and Deservedness Scale (PaDS) and the Dissociation Experience Scale (DES) were completed by participants and correlated with hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$). The data was shown to be reliable and valid. The principal component analysis allowed the extraction of two factors corresponding to visual and auditory experiences similar to those reported in a previous study (Morrison's et al., 2000).

The participants underwent structural and functional imaging investigations. For volumetric analysis 3D T1 sagittal images were obtained. FreeSurfer and CAT12 imaging tools were used to analyse the 3D T1 scans and to measure volumetric differences.

Three functional MRI tasks were performed (spoken and read language comprehension, face recognition, and (audio)visual detection). In the language comprehension task, participants either listened to a sentence or read it as a text. The task was chosen because it activates language centres that have previously been reported to be associated with (verbal) hallucinatory experiences (Dierks et al., 1999; Lennox et al., 2000; Shergill et al., 2004; Suzuki et al., 1993; Silbersweig et al., 1995; McGuire et al., 1993,1996). The face detection task was chosen because it stimulates visual areas and the perception of faces is one of the more common visual hallucinations (Busigny, 2010; Barton, 2008; Allison et al., 1994). In the (audio)visual detection task, participants were presented with a visual target on the screen. Either less than a second prior, simultaneously or after this target flashed on the screen, the participant was presented with a beep. Participants were instructed to ignore the beep and to respond as soon as possible by pressing a button when they observed the visual target. The (audio)visual task was chosen to test theories that link hallucinatory experience with a failure to inhibit task irrelevant brain areas (particularly auditory areas) Hugdahl and colleagues (2008,2009,2012).

8.1 Launay-Slade Hallucination Scale as an Instrument to Capture Visual and Auditory Hallucination Proneness

The distribution of the $LSHS_{(M)}$ was near-normal, see Figure 2.2, as reported in a previous study (R. P. Bentall & Slade, 1985). The factor analysis extracting two factors as recommended by Morrison et al. (2000). The total variance accounted for (45.96%) shown in Table 2.1 is higher than the 38% reported by Morrison et al. (2000). Cronbach's alpha coefficient was used to measure reliability and, for the entire scale = .845; previous studies have recommended that an alpha of .70 or above indicates acceptable reliability. The Two factors were extracted in a factor analysis, the first factor mapped onto questions that measure predisposition to auditory hallucination ($LSHS_{(A)}$) and included 6 items with an alpha coefficient of .74. The second factor measured predisposition to visual hallucination ($LSHS_{(V)}$) and also including 6 items with an alpha coefficient of .79. coefficient alpha analysis to measure the reliability for the 8 PaDS persecution item was .757 and for the DES with 27 removed was .924. A significant positive correlation was found between modified $LSHS_{(M)}$ scale and the DES as found as expected. Moreover, a significant positive correlation was also observed between auditory

($LSHS_{(A)}$) and visual ($LSHS_{(V)}$) scores and the DES. which is consistent with previous studies (Pilton et al. 2015). The participants data provide reliable data that can be separated into visual and auditory scores and matches previously reported data on this widely used scale. It therefore provides a good characterisation of hallucination proneness in our healthy population.

8.2 Brain Morphology

A common finding in psychotic patients is that brain areas associated with language processes have lower volume or thickness compared to controls, see Table (4.1, 4.2) for a summary of the literature. The continuum model therefore predicts that high hallucination proneness in the healthy population should be linked to lower volumetric measures in these brain areas in the healthy population. No significant *negative* correlation between the $LSHS_{(M)}$ scores and brain (volumes or thickness) were found in any of the target areas. Volumetric analysis using CAT12, instead, shows a significant *positive* correlation between $LSHS_{(M)}$ scores and bilateral transverse temporal gyrus volume as well as bilateral middle occipital gyrus. In addition, a separate surface based analysis, using FreeSurfer, showed a significant positive correlation between $LSHS_{(M)}$ scores and bilateral TTG and left Fusiform gyrus thickness. Moreover, the auditory experience related $LSHS_{(A)}$ scores positively correlated with thickness measures of bilateral TTG, left fusiform cortex and left precuneus. Similarly, $LSHS_{(V)}$ scores (visual) correlated positively with right TTG thickness and left MTG volume.

These results therefore are inconsistent with continuum model predictions on the basis of previous studies comparing patients with controls (Table 4.1 & 4.2). These studies show consistent decreases in brain grey matter volume and ventricular enlargement in schizophrenia patients (Haijma et al., 2013; Shepherd et al., 2012; De Moura et al., 2018). Volume reductions are typically seen in first episode psychosis (Chan et al., 2011; Shepherd et al., 2012) and several studies have also reported that the grey matter volume reductions are progressive (Andreasen et al., 2011; Chan et al., 2011; Haijma et al., 2013; Shepherd et al., 2012; van Haren et al., 2008). There are, however, a small number of studies that describe increases in brain volumes. Modinos et al. (2009) reported that the average of the cortical volume of the left frontal gyrus positively correlated with hallucination severity scores in

schizophrenia patients. Zhuo et al. (2020), in the only study that compared brain structure with hallucination proneness in healthy participants, observed a significant positive correlation between hallucination severity and gyrification in the left superior temporal gyrus, left temporoparietal junction, the superior frontal gyrus and the left parietal lobe in healthy people.

The link between brain structure and hallucination proneness in our healthy population is diametrically opposed to the predictions made by the continuum model on the basis of patient data. A possible explanation for this difference may lie in the characteristics of the sample populations. Some hallucinating patients, for example, may have received lithium or other antiepileptic medication, which has been shown to cause cortical thickness increases for shorter or longer lifetime cycles (Hibar et al., 2018). In contrast, the quantity of antipsychotic medication (sode years equal to 10 mg daily pf chlorpromazine) over the follow up period expected loss of brain volume (p=0.003 adjusted for symptom level, alcohol usage and weight again (Veijola et al., 2014). Moreover, several studies have shown that volumetric changes in the STG have been caused by psychotic symptoms (Kim et al., 2003) and periods of illness (Liao et al., 2015). Read et al. (2005) argued that the increase in the grey matter thickness may be a result of the traumagenic neurodevelopmental model, which attempts to integrate what is known about the neurobiology of psychosis with insights from studies of trauma victims, and argues that trauma leads to change in structures such as ventricular enlargement. In addition, Cahn et al. (2002) claimed the total brain volume (-1.2%) and cerebrum gray matter volume of (-2.9%) declined significantly and lateral ventricle volume increased substantially (7.7%) in schizophrenia patients. In addition, the authors report that the reduction in global gray matter volume matter was substantially associated with the outcome and, independently with consistently higher doses of antipsychotic drugs.

Social isolation is another possible cause for systematic differences between schizophrenia sufferers and healthy controls that may be reflected in behavioural changes, for example in terms of social interactions. Stahn et al. (2019) compared volumetric brain changes in antartic researchers who for 14 months at the German Neumayer III Station in the Antarctic and found a significant reduction in hippocampal, orbito-frontal and dorsolateral prefrontal cortex volume. Paulik (2012) indicated that the occurrence of AVH might be influenced by interpersonal interactions while Yanos et al. (2010) show that social interactions are an

important factor in the recovery of schizophrenia patients. Systematic sampling differences, therefore, may also explain structural differences that are the results of behavioural change caused by hallucinations rather than the cause of hallucinations.

8.3 functional MRI

8.3.1 Relevant tasks

literature suggests reduction in task-related activation for a range of fMRI tasks in patients relative to controls (discussed in chapter 5). Functional neuroimaging experiments using externally provided voice stimuli or guidance for generating internal speech in hallucination patients showed decreased neuronal activity relative to control in the same brain regions (Zhang et al., 2008) and compared to non-hallucination patients (McGuire et al., 1996). Moreover, visual task (faces) shows a reduction in the activation in the visual areas (Boubela et al., 2015). Therefore, the continuum model predicts that activation during speech comprehension, face processing and target detection should be negatively correlated with hallucination proneness measures.

fMRI studies using cross-modal stimuli, for example, showed deactivation in auditory cortices during visual stimulation, and visual deactivation during auditory tasks (Laurienti et al., 2002; Lewis et al., 2000). Therefore, the continuum model predicts that activation in language areas during visual stimuli will positively correlated with hallucination scales ($LSHS_{(M)}$ $LSHS_{(A)}$ and $LSHS_{(V)}$) scores.

Neuroimaging studies reported reduced (left lateralised) inferio-frontal activity during the performance of verbal fluency tasks (Curtis et al., 1998, Yurgelun-Todd et al., 1996, Artiges et al., 2000, Kim et al., 2000, Boksman et al., 2005, Kircher et al., 2002, Dollfus et al., 2005). Moreover, Language lateralization of the inferior frontal cortex is similarly reduced in medicated (Weiss et al., 2002) and unmedicated (Weiss et al., 2006) patients relative to healthy controls. Therefore, the continuum model predicts that reduce lateralization index activation during speech comprehension, also, lateralization index should be negatively correlated with hallucination proneness measures ($LSHS_{(M)}$ $LSHS_{(A)}$ and $LSHS_{(V)}$) scores.

8.3.1.1 Language comprehension task

No significant *negative* correlations were found between the hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V))}$ scores and activation patterns in the regions of interest in the language comprehension tasks. In the spoken language comprehension condition, instead, there was a positive correlation between $LSHS_{(M)}$ scores and activity in key language areas: the bilateral frontal gyrus and bilateral TTG. $LSHS_{(A)}$ scores were also positively correlated with bilateral TTG activation.

It might be argued that, since healthy hallucinators 'sit in the middle' of the continuum scale, the significant negative correlations seen in patients, might be there in the healthy population, but simply not reach the significance thresholds. The functional imaging results show consistent but insignificant *positive* correlations between the $LSHS_{(M)}$ scores and activation in task-related regions (TTG, STG, MTG, IFG, MFG). This means the failure to provide positive evidence for the continuum model is not a matter of 'missing significance critera' in the analysis, which already sets a low threshold because p-values are not corrected for multiple comparisons. The results were in line with previous studies, which reported more activation in patients with hallucinations compared to non-hallucination patients (Braver et al., 1997).

McGuire et al., 1996 argued that reading with distorted feedback of the subject increase activation in insula. Which paly role in misattribution the of non-self source. Those activation in the regions (superior temporal gyrus, inferior frontal gyrus and insula) associated with hallucination during reading (inner speech) may lead to failure on source monitoring. Moreover, Daprati et al., 2007 argued that hallucination is triggered by deficiencies in the immediate distinction between self-generated and external induced. Shergill et al., (2000) identified the clinical case experiencing recurrent auditory and somato-sensory hallucinations of varying duration. The analysis of regions of the brain active while hallucinations showed the proper activation of STG unique to the duration of auditory hallucinations.

8.3.1.2 Face detection task

The results for the face detection task mirror those seen for the language task. The key finding is that no significant *negative* correlation between any hallucination proneness measures ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and BOLD response in regions of interest was found.

The results, instead, show trend to a positive correlation between $LSHS_{(M)}$ scores and activity in middle occipital gyrus and superior occipital gyrus, which has previously been involved in the visual hallucinations, however, it does not reach to significant. This is in line with Zmigrod et al., 2016 results claimed, visual hallucination linked to visual cortex activity. Also, the Precuneus was also identified to be positively correlated with $LSHS_{(M)}$ scores. The Precuneus has been reported to be involved in the integration of visuospatial imagery, processing of self-centred mental imagery strategies and to separate body image from external space; impairments in which results in the development of hallucinations (Pagonabarraga et al., 2014). Studies found that Precuneus was activated during visual hallucinations (Silbersweig et al., 1995) and that patients with hallucinations demonstrated increased activation in the Precuneus (Oertel et al., 2007); in line with the findings from this study.

A positive correlation in the faces task was identified between hallucination severity scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and the fusiform activation, indicating that the participants in the high hallucination proneness group exhibited high activation in the fusiform, however, it does not reach to significant. This consistent with (Kensinger and Schacter., 2005) results, and this brain region (Fusiform) was also associated with visual imagery. Furthermore, visual hallucination may consist of the reoccurrence of visual memory-based mental images misinterpreted (Barnes, 2015; Bentall, 1990). Another explanation, the visual hallucination is a result of increase activation in the ventral occipital lobe (superior occipital gyrus and middle occipital gyrus) which in line with (Ffytche et al., 1998) study.

8.3.1.3 (Audio)Visual detection task

No significant negative correlations were found between the hallucination proneness scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and activity in regions of interest for the audio/visual task (appendix B4-1). This means the data does not provide positive support for the continuum theory. The results, instead, show a trend to positive correlation between the functional activation and LSHS scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) in the visual cortex (Precuneus, SOG

and MOG), indicating that the participants in the high hallucination proneness group exhibited high activation in the visual cortex.

The result is consistent with Daselaar et al., 2010 finding. The result is in line with (Ishai et al., 2000; Kosslyn, 2000; Suchan et al., 2002) finding, greater activation in precuneus during visual task in AVH patients compare to healthy. The precuneus is involved visuospatial working memory or attention (Culham & Kanwisher., 2001).

These finding on task-relevant functional activation for all tasks are the opposite of the continuum model predictions based on the literature, in chapter 5, which shows that the majority of patient studies show that reduced functional activation in task-relevant areas is seen in patients suffering from hallucinations. The results presented here for healthy participants also run counter to data reported by Plaze et al. (2006) who showed a *negative* correlation between hallucination severity and brain activity in the left superior temporal gyrus while AVH patients listened to sentences.

A systematic quantitative review exploring neural dysfunction in controls and healthy participants who were at high clinical risk (HCR) of psychosis highlights that functional activation patterns in the healthy population are far from clear-cut (Dutt et al., 2015). Their review of 22 studies covering a number of cognitive tasks showed that, for language processing tasks, reported increases in activation in the HCR were as common as decreases in MFG and IFG, and ITG while decreased activation was commonly seen in short and long term verbal memory tasks were commonly seen MTG. Across 19 brain areas, they showed 56 reports of reduced functional activation compared to 37 reports of relative activation increases for the HCR group. Given that fMRI studies are based on very variable participant numbers, varying quality control and different significance thresholds, it may well be argued that a direct comparison of 'identified clusters' is not particularly meaningful, especially over a wide range of tasks and brain regions. The study, however, highlights that clear-cut data for the at-risk group, currently does not exist. The data presented here does is not what the continuum predicts from the patient data, but is at least not inconsistent with a number of studies showing increased functional activation for a range of cognitive tasks in the healthy at-risk group.

It might be argued that, since healthy hallucinators 'sit in the middle' of the continuum scale, the significant negative correlations seen in patients, might be there in the healthy population, but simply not reach the significance thresholds. The functional imaging results

show consistent but insignificant positive correlations between the LSHS(M) scores and activation in task-related regions, see Tables in the appendix for chapter 5 (C1-1, C1-2, C1-3, C2-1, C2-2, C2-3, C3-1, C3-2 and C3-3). This means the failure to provide positive evidence for the continuum model is not a matter of a failure to 'reach significance criteria' in the analysis, which already sets a low threshold because p-values are not corrected for multiple comparisons.

8.3.2 Inhibition of task-irrelevant brain areas

A failure to inhibit auditory signals, whether behaviourally (Hughes et al., 2012) or neurophysiological (Ford et al., 2012) is the basis for a number of explanations of AVH. The continuum model predicts increased activation in task irrelevant, especially language related, areas.

A significant positive correlation between the $LSHS_{(V)}$ score and activation in right superior temporal gyrus (STG) was found for the face recognition task. Furthermore, there was a significant positive correlation between $LSHS_{(A)}$ scores and functional activation in the right IFG, STG MTG while participants performed the audio/visual task.

These results are in line with the hypothesis: reduced inhibition in non-task relevant areas in high hallucination proneness. The results in line with Waters et al. (2003) findings. Moreover, the results replicate Badcock et al. (2015) findings, there is a relation between planned inhibition struggles and hallucination experiences. Healthy prone to hallucinations shows challenges in the volunteer inhibition the currently irrelevant activation. In contrast, previous studies suggested that these participants during the visual task tried to ignore or deactivate irrelevant task activation in the temporal lobe (Ciaramitaro et at., 2007; Johnson & Zatorre, 2005).

This is the only task and neuroimaging metric where the observed behaviour matches the prediction.

Overview, executive and inhibitory regulation dysfunctions have been related to auditory hallucination. Inhibition deficiencies have also been associated with a decreased sense of control involved with auditory hallucination. theoretically, deliberate avoidance deficiencies can trigger mental experience to be perceived as unintentional and intrusive. Water et al. (2006) a deficit of anticipatory representation can also lead to this decreased sense of control.

Awareness and change deficits may play a completely different function, by specifying the perceptions and resources to allocated to these unintended auditory signals and by restricting the capacity to redirect and pass attention to other adaptive details (water et al., 2012).

8.3.3 Lateralization Index (LI)

Reduced lateralisation for language tasks has been proposed as a correlate of hallucinatory experiences in patients. If a continuum between healthy voice hearers and patients exists a negative correlation of LSHS scores with the Lateralisation Index, in specific areas (IFG, MFG, SFG, TTG, STG, MTG and ITG). No significant negative correlation found between the lateralization index and the hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores in any of the target areas. This means that the data reported here does not match the continuity model prediction of more bilateral activation (lower LI) with increasing hallucination proneness. In contrast, the analysis revealed no significant correlation between LI and all LSHS measures in IFG, MFG, TTG, STG, MTG, ITG. However, the results were trend to a positive correlation between LI and hallucination scales scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$).

This study result that decrease lateralization in healthy hallucination proneness subjects is due to a related increase in the right hemisphere is consistent with finding from other in AVH patients (Sommer et al., 2001b; Sommer et al., 2003). (Annett, 1992) claimed that right hemisphere growth of language related regions is responsible for the normal cerebral asymmetry in healthy subjects. It was therefore suggested to experiences an abnormality in this right hemisphere change linked to psychosis in patients (Crow, Done, & Sacker, 1996). (Leitman et al., 2007) suggested increase right side activation within the group of schizophrenia during language task can also reflect known abnormalities prosodic process.

8.3.4. Functional activation studies summary

The results are inconsistent with the first hypothesis (relevant task). None of the correlations between activation and LSHS scores were negatively significant as predicted by the continuum theory. However, none of the correlations were significant. The results instead, show a positive correlation between hallucination severity scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and relevant activation tasks in the (voice & text, faces and audio/visual), however, it does

not reach significant. The temporal region (TTG, STG and MTG) activation in the voice & text task toward to a positive correlated with hallucination proneness, and in occipital regions (MOG and SOG) and fusiform cortex, fMRI activation in the faces and audio/visual tasks was also toward to a positive correlated with hallucination proneness.

The results are inconsistent with the second hypothesis (inhibition). The results for the second hypothesis show a significant positive correlation between the ($LSHS_{(V)}$) and irrelevant (inhibition) in the language-related regions in the faces task. In addition, the results show a significant positive correlation between $LSHS_{(A)}$ scores and functional activation in the right IFG, STG MTG while participants performed the audio/visual task. All other data shows correlation toward to positive between hallucination scales and regions activation in the language areas (faces and audio/visual tasks) but not reach to significant.

The results are inconsistent with the third hypothesis (lateralization index). The results show no significant correlation between the lateralization index in the language-related regions (IFG and TTG) and the ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores.

8.4 White matter microstructure

8.4.1 Diffusion Tensor Imaging (DTI)

In the microstructural brain metrics predict that the hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores will negatively correlated with FA values and positively correlated with diffusivity measures (MD, AD and RD) in the regions related auditory and visual hallucination Microstructural measures of the brain derived from DTI analysis correlated with the $LSHS_{(M)}$ scores. No significant negative correlation found between the hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores and the FA, or positive correlation between hallucination scale and MD, AD and RD in the regions of interest related. The results instead, shows MD values correlated significantly negative with $LSHS_{(M)}$ scores in the inferior longitudinal fasciculus right (ILF_RT), superior longitudinal structure fasciculus right (SLF_RT) and occipital lobe (OL). Moreover, a significant correlation between $LSHS_{(M)}$ scores and RD values was identified in the OL. Finally, AD values demonstrated a significant negative correlation with $LSHS_{(M)}$ scores in the LT and RT SLF, ILF_RT and OL. However, the FA values of areas previously associated with hallucinations showed no significant correlation with $LSHS_{(M)}$ scores.

These results are inconstant with previous findings, which demonstrated an increase in MD, AD and RD values (Abdul-Rahman, Qiu, & Sim, 2011; Zhang et al., 2018). This study identified a major change to the WM in the frontal and temporal areas, which consists of long association fibre tracts such as the SLF and ILF. The significant reductions of AD, MD and RD in the SLF and ILF indicate the presence of frontotemporal disconnectivity of WM in participants with high hallucination proneness (Burns et al., 2003; Lawrie et al., 2002). On white matter structure, the negative correlation identified between $LSHS_{(M)}$ scores and MD, RD and AD values. This finding is further supported by the identified change in the left AF and the negative correlation between AD and MD values with $LSHS_{(M)}$ scores. The results from this study suggest that hallucinations are associated with a complex set of white matter abnormalities, cortical changes and functional impairment in brain areas related to language. The changes in the white matter in the DTI and tractography within the SLF, ILF and AF, which connect the frontal and temporal areas, likely contribute to the development of auditory hallucinations. Because connection between the frontal lobes, where speech and verbal thoughts are produced, and the temporal lobes, where they are perceived are dysfunction and failure to recognise inner speech (Ford, Mathalon, Whitfield, Faustman, & Roth, 2002) . Moreover, the identified changes to white matter in the occipital lobe, are hypothesised to contribute to visual hallucinations. Because of alteration in the tract communicate between temporal and occipital regions, leads to impaired in visual function (Rafique, Richards, & Steeves, 2018).

8.4.2 Tractography Arcuate Fasciculus (AF)

In the is chapter the results as predicted to be a negative correlation between hallucination scales scores ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and FA and tract volume. Also, a positive correlation between hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and diffusivity measures (MD, AD and RD).

The arcuate fasciculus tract (AF) for the left and right side of the brain was extracted. The indices of the AF (FA, MD, AD, RD, tract volume and tract length) were correlated with the $LSHS_{(M)}$ score and subscales of $LSHS_{(A)}$ and $LSHS_{(V)}$ scores. No significant positive correlation found between the hallucination scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) scores and the FA and

tract length or positive correlation between the hallucination scales and MD, AD, RD and tract volume as predicted by the continuum theory. The results instead show, a significant negative correlation in MD and AD values with $LSHS_{(M)}$ scores in the left AF. However, the mean of tract volume and length values for the right and left AF showed no significant correlation with $LSHS_{(M)}$ scores. Moreover, the mean of FA values for the right and left AF showed no significant correlation with $LSHS_{(M)}$ scores. Interestingly, previous reports are discrepant in terms of the direction of changes of FA values reported with some reporting a decrease in FA (Abdul-Rahman et al., 2012; Catani et al., 2011; Ćurčić-Blake et al., 2015; De Weijer et al., 2011; Knöchel et al., 2012; McCarthy-Jones et al., 2015). Fractional Anisotropy (FA) is a measure of tract integrity. The correlation between the $LSHS_{(M)}$ scores and AF indices were significant in the left hemisphere, in line with previous studies (Chawla, Deep, Khandelwal, & Garg, 2019). Dooley et al. (2019) reported a similar correlation as reported in this study, decrease in the mean diffusivity value in AVH patients compared to healthy. However, Falkenberg et al. (2019) reported a significant longer tract along the AF in patients with AVH compare to healthy. (Jardri et al., 2011; Kompus et al., 2011) argued that increase in the length of the arcuate fasciculus fiber could promote neuronal interaction between AF linked regions in the temporal frontal lobes, which may in turn lead to some kind of functional hyperactivity in these areas through hallucinatory episodes.

Based on the results obtained in this study, we suggested that the differences in the MD and AD of the AF, which connects frontal regions with temporal areas, may cause hallucinations. The greater leftward lateralization correlation of (FA, tract volume and tract length) in the left Arcuate Fasciculus (AF) with hallucination severity scales may be explained relative deficiency in the bundle with right Arcuate Fasciculus compared to the left in the high hallucination proneness. Thus, the discrepancy between the white matter consistency of the left Arcuate Fasciculus and the accentuation of the normal left larger than the right Arcuate Fasciculus indicates an aberrant fronto-temporal connectivity. The hyperconnectivity between frontal and temporal brain regions can affect corollary discharge of neural signals from frontal speech areas to auditory cortex (Abdul-Rahman et al., 2012). Moreover, this abnormal connectivity between the frontal and temporal lobe lead to facilitate functional imbalance between language production and language perception areas (Rotarska-Jagiel et al., 2009).

8.4.3 White Matter Microstructure Results Justification

The increase in the FA value and decrease in MD and AD value reflects the status of the myelination in white matter. In this study the FA increased, and MD and AD decreased, which mean thicker myelination. The explanation for this result is that the Oligodendrocytes cells responsible for the myelination of axon increased (Rios et al., 2003). As oligodendrocytes mature their processes, build a myelin sheath which repeatedly envelops and then compacts a segment of the axon (Kipp et al., 2012). The process occurs across the axon diameter frequently remyelinated along the axon which reduce the axon diameter (AD). One of the reasons increase the mature oligodendrocytes is the voluntary exercise for example running (Krityakiarana et al., 2010). So, it can be the participants who running frequently the remyelination increase and lead to a reduced axon diameter, which increase the FA and decrease MD and AD values. Another reason lead to increase the proportion of the myelination axon is the social enrichment (Juraska and Kopcik, 1988). The brain structure hypermyelination or oligodendrocytes generate further during more socialise (Makinodan et al., 2012). Which mean the people scores high in the $LSHS_{(M)}$ were more socialise and leaded to increase the myelination axons.

8.5 Continuum hypothesis

There was a correlation between the hallucination severity scales ($LSHS_{(M)}$, $LSHS_{(A)}$ and $LSHS_{(V)}$) and brain structures and functional in hallucination proneness. However, the results were opposite to the literature and failure to prove the continuum theory. It might therefore be argued that the sample used in this study did not span the range of hallucinatory experiences. An analysis of the $LSHS_{(M)}$ scores for our population is presented in chapter 3 and shows that both the range of responses and the factor structure matches data recorded elsewhere. The sample size also is larger than that used in many other imaging studies. These two factors, taken together, make 'sampling effects' an unlikely explanation for the failure to find significant support for the continuum hypothesis. The novelty in this study is the results in the structures and functional is opposite to the literature. Moreover, the inconsistent results noticed in all the empirical chapters ($LSHS_{(M)}$, Volumetric, fMRI, DTI and tractography).

8.6 Limitation

The aim of this study was to see if volumetric, microstructural and functional differences previously described between hallucinating SZ patients and controls predict hallucination proneness in the healthy population. There is some variability in the patient data and a direct comparison between our data and the patient data is further complicated by the range of diagnostics that are used to identify participants in other studies. A more direct comparison of a large mixed group of healthy participants and patients, in both groups with and without AVH, of hallucination proneness would help to answer the question whether hallucination proneness really presents on a continuum and whether other, independent, factors predict psychosis.

There are many other factors not addressed related to structure changes. (Narr et al., 2007) reported a positive correlation between gray matter measurements and full-scale intelligence quotient in healthy adults, which is not included in this study. In addition, the Social enrichment (Juraska and Kopcik, 1988) has also been linked to increases in myelination. The brain structure hypermyelination or oligodendrocytes generate further during more socialise (Makinodan et al., 2012). Which mean the people scores high in the $LSHS_{(M)}$ were more socialise and leaded to increase the myelination axons. Furthermore, Voluntary exercise, for example running, has been linked to increased oligodendrocyte maturation (Krityakiarana et al., 2010). It is therefore possible that reductions in the FA and increases of MD and AD values, which have been reported for psychotic patients, are directly linked to behavioural differences, for example the engagement in sports. Finally, traumagenic linked to the brain structures changes. Through found increase the ventricle as a result of trauma during childhood (Read et al., 2005).

8.7 Future Studies

Further research is needed to study the usefulness of the $LSHS_{(M)}$ questionnaire to investigate the relationship between hallucination proneness and brain structure and function in non-hallucination healthy family and patients. If there is a similarity in brain structure (as one might expect) then perhaps that suggests that the differences seen between patients, healthy but non-hallucinating family members, and healthy controls provide an explanation for

psychosis – independent of hallucinations. Furthermore, the limitation in this study could be considered such as social isolation, history of trauma, full-scale intelligence quotient and (running activity or strength training).

8.8 Conclusion

In conclusion, the $LSHS_{(M)}$ shows a reliability to measure predisposition toward the auditory and visual hallucination proneness. In addition, other subscales ($LSHS_{(A)}$ and $LSHS_{(V)}$) shows a reliability to measure susceptibility toward the auditory and visual hallucination proneness. The volumetric measurement shows showed a significant positive correlation between $LSHS_{(M)}$ scores and bilateral TTG and left Fusiform gyrus thickness in the FreeSurfer results. Also, shows a significant *positive* correlation between $LSHS_{(M)}$ scores and bilateral transverse temporal gyrus volume as well as bilateral middle occipital gyrus in CAT12 results. No significant correlation found between hallucination scales and relevant tasks in (voice & text, faces and audio/visual). A significant correlation found between $LSHS_{(A)}$ and right STG in faces task. Furthermore, a positive correlation found between $LSHS_{(V)}$ scores and right (IFG, STG MTG) while participants performed the audio/visual task. No negative correlation found between lateralization index and hallucination severity scales. The DTI results shows MD values correlated significantly negative with $LSHS_{(M)}$ scores in the (ILF_RT), (SLF_RT) and (OL). Moreover, a significant correlation between $LSHS_{(M)}$ scores and RD values was identified in the OL. Finally, AD values demonstrated a significant negative correlation with $LSHS_{(M)}$ scores in the LT and RT SLF, ILF_RT and OL. The tractography of the arcuate fasciculus results shows a significant negative correlation in MD and AD values with $LSHS_{(M)}$ scores in the left AF. The novelty in this study that multimodal neuroimaging measurements performed in the same data collected to test the hypothesis.

In the vast majority of the datasets provide NO evidence for the continuum hypothesis – the only exception is that (audio)visual task where high scorers show significantly more activation in auditory regions when they should actively suppress auditory signal representations because they are not task-relevant. Everywhere else we see either no significant correlations or correlations that are going in the opposite direction.

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Appendices

A1: The $LSHS_{(M)}$ scale to capture visual and auditory hallucination proneness (Morrison et al., 2000).

1-Sometimes a passing thought will seem so real that it frightens me.
2-Sometimes my thoughts seem as real as actual events in my life.
3-No matter how hard I try to concentrate; unrelated thoughts always creep into my mind.
4-In the past I have had the experience of hearing a person's voice and then found that no one was there.
5-The sounds I hear in my daydreams are usually clear and distinct.
6-The people in my daydreams seem to true to life that I sometimes think they are.
7-In my daydreams I can hear the sound of a tune almost as clearly as I was listening to it.
8-I often hear a voice speaking my thoughts aloud.
9-I have been troubled by hearing voices in my head.
10- On occasions I have seen a person's face in front of me when no one was in fact there.
12-In the past I have heard the voice of God specking to me.
13- When I look at things, they appear strange to me.
14-I see shadows and shapes when there is nothing there.
15- When I look at things, they look unreal to me.
16- When I look at myself in the mirror, I look different.

A2: PaDS paranoid measurements scale.

1-My friends often tell me to relax and stop worrying about being deceived or harmed.
2-Sometimes, when I am out in public, I feel that people might be talking about me.
3-I'm often suspicious of other people's intentions towards me.
4-People will almost certainly lie to me.
5-I often worry about being criticized or rejected in social situations
6-I believe that some people want to hurt me deliberately.
7-You should only trust yourself.
8-Sometimes I think there are hidden insults in things that people say or do.
9-I deserve to be disliked by other people.
10-Because of the sort of person I am, people have good reasons to want to harm me.

A3: The Dissociative Experiences Scale.

1-Some people have the experience of driving a car and suddenly realizing that they don't remember what has happened during all or part of the trip.
2-Some people find that sometimes they are listening to someone talk and they suddenly realize that they did not hear all or part of what was said.
3-Some people have the experience of finding themselves in a place and having no idea how they got there.
4-Some people have the experience of finding themselves dressed in clothes that they don't remember putting on.

5-Some people have the experience of finding new things among their belongings that they do not remember buying.
6-Some people sometimes find that they are approached by people that they do not know who call them by another name or insist that they have met them before.
7-Some people sometimes have the experience of feeling as though they are standing next to themselves or watching themselves do something as if they were looking at another person. 8-Some people are told that they sometimes do not recognize friends or family members.
9-Some people find that they have no memory for some important events in their lives (for example, a wedding or graduation).
10-Some people have the experience of being accused of lying when they do not think that they have lied.
11-Some people have the experience of looking in a mirror and not recognizing themselves.
12- Some people sometimes have the experience of feeling that other people, objects, and the world around them are not real.
13- Some people sometimes have the experience of feeling that their body does not belong to them.
14-me people have the experience of sometimes remembering a past event so vividly that they feel as if they were reliving that event.
15-Some people have the experience of not being sure whether things that they remember happening really did happen or whether they just dreamed them.
16-Some people have the experience of being in a familiar place but finding it strange and unfamiliar.
17- Some people find that when they are watching television or a movie they become so absorbed in the story that they are unaware of other events happening around them.
18- Some people sometimes find that they become so involved in a fantasy or daydream that it feels as though it were really happening to them.
19- Some people find that they are sometimes able to ignore pain.
20-Some people find that they sometimes sit staring off into space, thinking of nothing, and are not aware of the passage of time.
21- Some people sometimes find that when they are alone they talk out loud to themselves.
22- Some people find that in one situation they may act so differently compared with another situation that they feel almost as if they were different people.
23 Some people sometimes find that in certain situations they are able to do things with amazing ease and spontaneity that would usually be difficult for them (for example, sports, work, social situations, etc.).
24-Some people sometimes find that they cannot remember whether they have done something or have just thought about doing that thing (for example, not knowing whether they have just mailed a letter or have just thought about mailing it).
25- Some people find evidence that they have done things that they do not remember doing.
26-Some people sometimes find writings, drawings, or notes among their belongings that they must have done but cannot remember doing.
27-Some people find that they sometimes hear voices inside their head that tell them to do things or comment on things that they are doing
28- Some people sometimes feel as if they are looking at the world through a fog so that people or objects appear far away or unclear.

Appendix B

B1: Previous studies show structures alteration in the hallucination patients.

Authors	Participants	Regions of interest	Results
Lutterveld, 2017	50 AVH patients 50 Non-AVH patients	LT Pars orbitalis LT Paracentral lobule RT Fusiform gyrus RT Inferior temporal gyrus RT insula	AVH patients ↓ thickness in (pars orbitalis, paracentral lobule, fusiform gyrus, ITG, insula).
Cierpka, 2017	10 AVH patients 10 Non-AVH patients	Cerebellum	AVH patients ↓ thickness.
Kubera, 2014	10 AVH patients 10 Non-AVH patients	MFG, IFG, STG, Insula, IPL, TTG, ITG, MTG, postcentral gyrus, fusiform gyrus and Lingual gyrus.	AVH patients ↓thickness in (MFG, IFG, STG, Insula, IPL, TTG, ITG, MTG, postcentral gyrus, fusiform gyrus, Lingual gyrus).
Chen, 2015	18 AVH patients 31 Non-AVH patients	RT Heschl's gyrus	AVH patients ↓ thickness
Cui, 2017	115 AVH patients 93 Non-AVH patients	LT MTG	AVH patients ↓ thickness LT MTG
Morch-Johnsen, 2017	145 AVH patients 49 Non-AVH patients	LT Heschl's gyrus, planum temporal and STG.	AVH patients ↓ thickness of LT Heschl's gyrus.
Neves, 2016	9 AVH or visual hallucination patients 12 Non-hallucinate patients	Orbitofrontal cortex, prefrontal areas, cingulate gyrus, fusiform gyrus, superior temporal cortex, amygdala, insula, thalamus and temporal lobe.	AVH or visual hallucination patients ↓ thickness RT posterior insula.
Lutterveld, 2014	50 AVH patients 50 Non-AVH patietns	LT paracentral cortex, LT pars orbitalis, RT fusiform gyrus, RT ITG and RT Insula.	AVH patients ↓ thickness LT paracentral cortex, LT pars orbitalis, RT fusiform gyrus, RT ITG, and RT insula.
Ffytche, 2017	21 Visual hallucination (Parkinson disease) 286 Non-visual hallucination (Parkinson disease)	RT supramarginal gyrus, superior frontal cortex, lateral occipital cortex.	AVH patients ↓ thicker RT supramarginal gyrus, superior frontal cortex and lateral occipital cortex.
Shin, 2005	17 AVH patients 8 Non-AVH patients	Frontal, parietal and temporal lobe.	AVH patients ↑ thickness in frontal and temporal lobe
Palaniyappan, 2012	350 patients Meta analysis	bilateral insula, LT, bilateral STG and LT ITG.	Negative correlation between hallucination severity and (bilateral insula, bilateral STG and LT ITG).
Sumich, 2005	25 AVH patients 12 healthy	LT heschl's gyrus	AVH patients ↓ thickness LT heschl's gyrus.
Onitsuka, 2004	23 AVH patients 28 healthy	LT STG and MTG.	AVH patients ↓ thickness in LT STG and MTG.

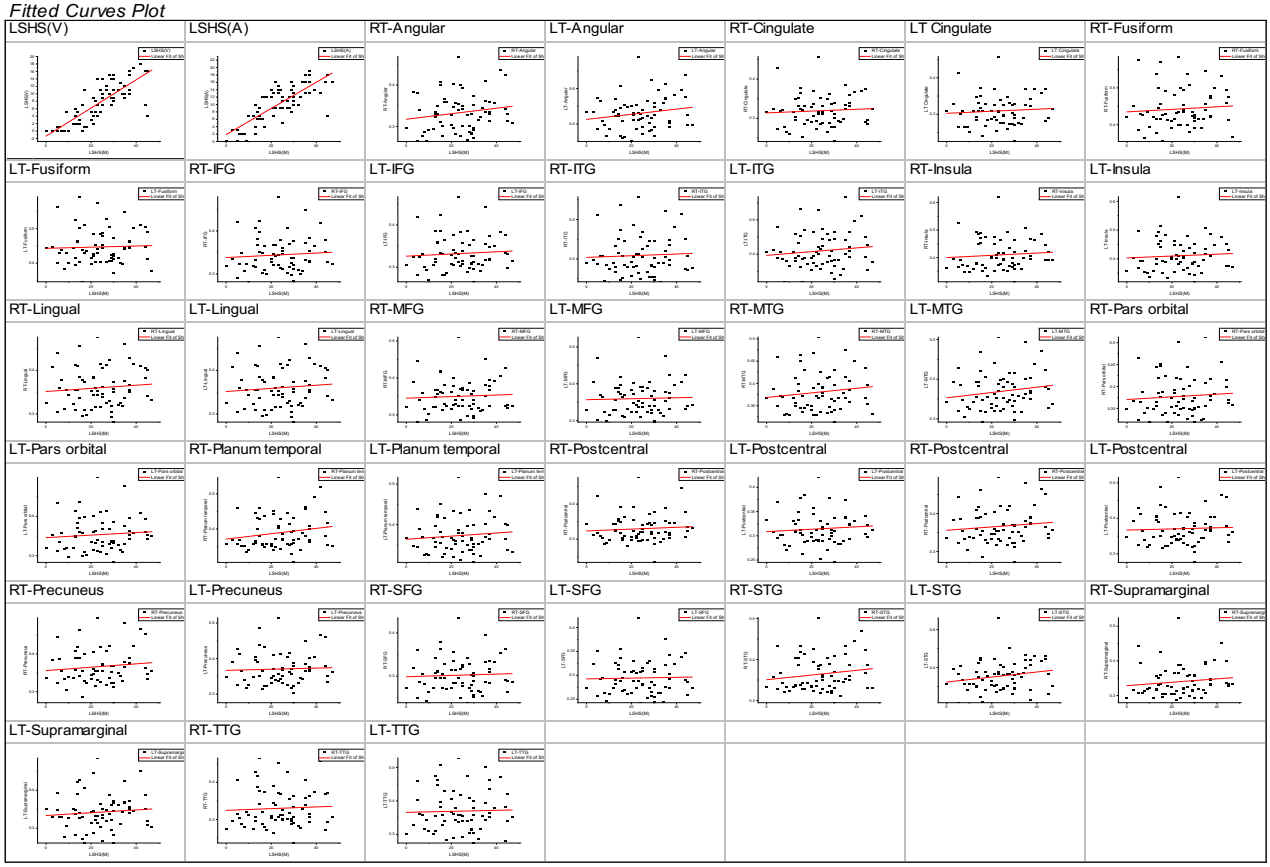
Nenadic, 2010	99 AVH patients	Bilateral STG, LT angular gyrus, LT postcentral gyrus.	Correlation with severity scale in bilateral STG, LT angular gyrus, LT postcentral gyrus.
Van Tol, 2014	31 AVH patients 20 Non-AVH patients	LT STG, LT IFG, RT parahippocampal gyrus.	AVH patients ↓ volume LT STG and LT IFG and RT parahippocampal.
Modinos, 2009	26 AVH patients	LT IFG	AVH patient's LT IFG volume positive correlated with hallucination severity.
O'Daly, 2007	28 AVH patients 32 healthy	Insula, RT STG, fusiform gyri and LT ITG.	AVH patients ↓ volume in insula, RT STG, fusiform, LT IFT.
Gaser, 2004	85 patients	LT TTG, Supramarginal gyrus,	AVH patients RT MFG, RT IFG, LT TTG and LT supramarginal gyrus.
Shapleske, 2002	41 AVH patients 31 Non-AVH patients	Insula, anterior cingulate precuneus.	AVH patients ↓ thickness insula, anterior cingulate Precuneus.
Van Swam, 2012	10 AVH patients 10 Non-AVH patients	LT Heschl's gyrus, bilateral STG.	AVH patients ↓ thickness LT Heschl's gyrus, bilateral STG.

Appendix B

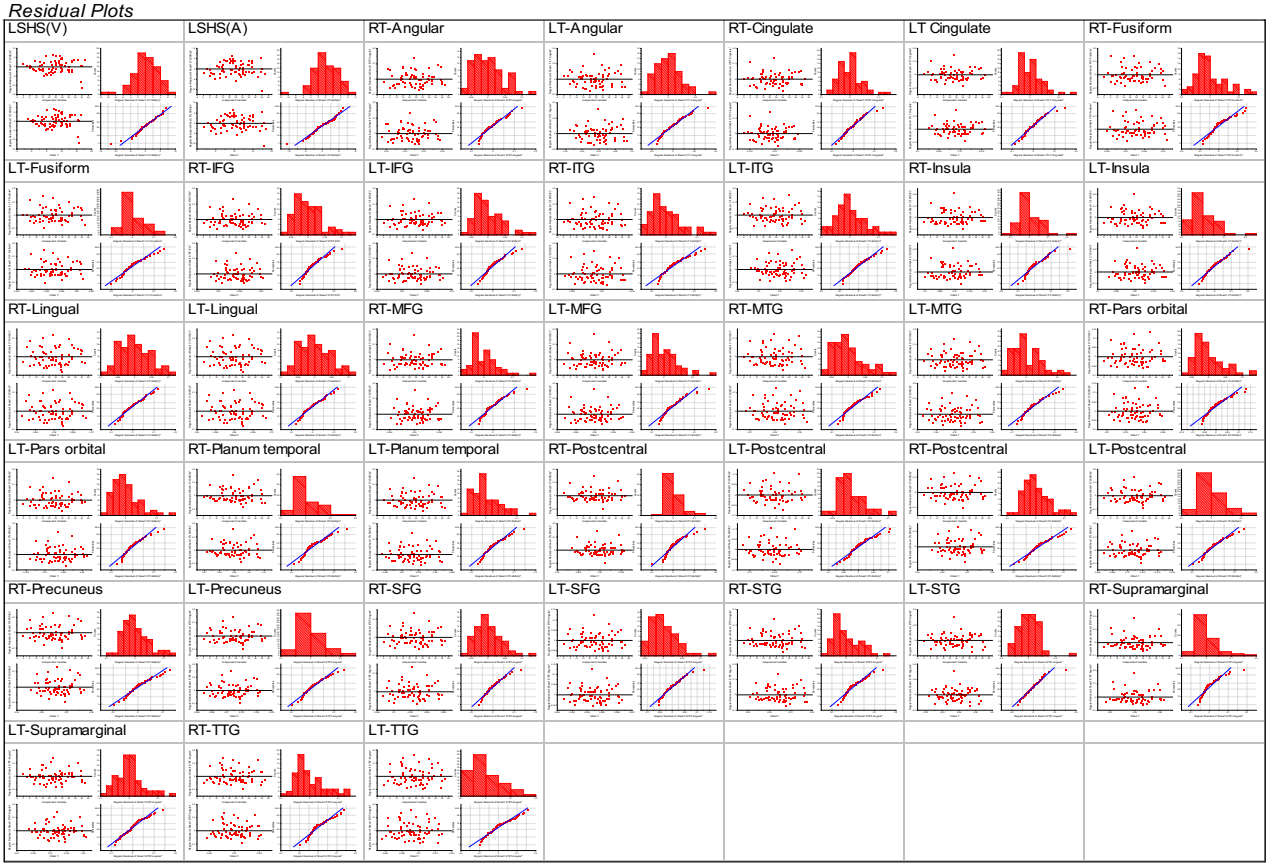
B1: CAT 12 result correlation with $LSHS_{(M)}$.

		Value	Standard Error	t-Value	Prob>|t|
LSHS(V)	Intercept	-1.36531	0.93871	-1.45445	0.15056
	Slope	0.37782	0.03543	10.66391	5.3656E-16
LSHS(A)	Intercept	1.86273	0.9114	2.04381	0.04497
	Slope	0.35419	0.0344	10.29671	2.30349E-15
RT-Angular	Intercept	0.31754	0.01258	25.23876	1.27878E-35
	Slope	6.63217E-4	4.74852E-4	1.39668	0.16719
LT-Angular	Intercept	0.42541	0.02593	16.40706	5.58284E-25
	Slope	0.00145	9.78612E-4	1.48423	0.14251
RT-Cingulate	Intercept	0.31387	0.01119	28.03943	2.21001E-38
	Slope	2.2743E-4	4.22486E-4	0.53831	0.59217
LT Cingulate	Intercept	0.30261	0.01144	26.45871	7.47633E-37
	Slope	2.8185E-4	4.31662E-4	0.65294	0.51606
RT-Fusiform	Intercept	0.43488	0.01477	29.43689	1.12727E-39
	Slope	3.43972E-4	5.57582E-4	0.6169	0.53942
LT-Fusiform	Intercept	0.44307	0.01416	31.29301	2.59944E-41
	Slope	1.66265E-4	5.34385E-4	0.31113	0.75668
RT-IFG	Intercept	0.33815	0.0113	29.91324	4.20261E-40
	Slope	2.61677E-4	4.26659E-4	0.61332	0.54178
LT-IFG	Intercept	0.32607	0.01148	28.3924	1.03008E-38
	Slope	2.57236E-4	4.33452E-4	0.59346	0.5549
RT-ITG	Intercept	0.40376	0.01402	28.79664	4.3398E-39
	Slope	2.14475E-4	5.29188E-4	0.40529	0.68657
LT-ITG	Intercept	0.39642	0.01451	27.32628	1.0596E-37
	Slope	5.44282E-4	5.47525E-4	0.99408	0.32382
RT-Insula	Intercept	0.39983	0.01561	25.60657	5.36967E-36
	Slope	4.10766E-4	5.89324E-4	0.69701	0.48824
LT-Insula	Intercept	0.40305	0.01519	26.53775	6.24351E-37
	Slope	3.24176E-4	5.73226E-4	0.56553	0.57363
RT-Lingual	Intercept	0.35145	0.01262	27.84791	3.35554E-38
	Slope	3.61641E-4	4.76322E-4	0.75924	0.45041
LT-Lingual	Intercept	0.35145	0.01262	27.84791	3.35554E-38
	Slope	3.61641E-4	4.76322E-4	0.75924	0.45041
RT-MFG	Intercept	0.34531	0.0123	28.07892	2.02831E-38
	Slope	2.11865E-4	4.64158E-4	0.45645	0.64956
LT-MFG	Intercept	0.35684	0.01252	28.49717	8.22508E-39
	Slope	1.32158E-4	4.72608E-4	0.27964	0.78063
RT-MTG	Intercept	0.36845	0.01258	29.28841	1.53752E-39
	Slope	5.17711E-4	4.74804E-4	1.09037	0.27952
LT-MTG	Intercept	0.35302	0.01293	27.30219	1.11789E-37
	Slope	6.69492E-4	4.88017E-4	1.37186	0.17475
RT-Pars orbital	Intercept	0.37039	0.01228	30.16723	2.49714E-40
	Slope	3.03073E-4	4.63397E-4	0.65402	0.51537
LT-Pars orbital	Intercept	0.346	0.01199	28.86796	3.73004E-39
	Slope	3.22029E-4	4.52367E-4	0.71187	0.47905
RT-Planum temporal	Intercept	0.37137	0.01338	27.76106	4.05847E-38
	Slope	7.61611E-4	5.04895E-4	1.50845	0.13621
LT-Planum temporal	Intercept	0.364	0.01212	30.03024	3.30502E-40
	Slope	3.86049E-4	4.57483E-4	0.84386	0.4018
RT-Postcentral	Intercept	0.32338	0.01119	28.89908	3.49185E-39
	Slope	2.61219E-4	4.22338E-4	0.61851	0.53837
LT-Postcentral	Intercept	0.30855	0.00983	31.39438	2.12779E-41
	Slope	2.49165E-4	3.70944E-4	0.6717	0.50412
RT-Postcentral	Intercept	0.35584	0.01277	27.85524	3.3022E-38
	Slope	4.44415E-4	4.82146E-4	0.92174	0.36002
LT-Postcentral	Intercept	0.36689	0.01289	28.45357	9.03183E-39
	Slope	1.61534E-4	4.86663E-4	0.33192	0.741
RT-Precuneus	Intercept	0.35584	0.01277	27.85524	3.3022E-38
	Slope	4.44415E-4	4.82146E-4	0.92174	0.36002
LT-Precuneus	Intercept	0.36689	0.01289	28.45357	9.03183E-39
	Slope	1.61534E-4	4.86663E-4	0.33192	0.741
RT-SFG	Intercept	0.29868	0.01083	27.58035	6.0383E-38
	Slope	1.50205E-4	4.08734E-4	0.36749	0.71443
LT-SFG	Intercept	0.29244	0.0098	29.83239	4.96406E-40
	Slope	8.23206E-5	3.69978E-4	0.2225	0.82461
RT-STG	Intercept	0.35068	0.01186	29.55822	8.75634E-40
	Slope	5.74265E-4	4.47782E-4	1.28247	0.20417
LT-STG	Intercept	0.32375	0.02146	15.08787	4.47537E-23
	Slope	0.00132	8.09872E-4	1.63431	0.10695
RT-Supramarginal	Intercept	0.32851	0.01254	26.18957	1.38562E-36
	Slope	4.88326E-4	4.73422E-4	1.03148	0.30608
LT-Supramarginal	Intercept	0.3335	0.01291	25.83664	3.13676E-36
	Slope	3.6792E-4	4.8718E-4	0.7552	0.45281
RT-TTG	Intercept	0.32453	0.01453	22.34261	1.73428E-32
	Slope	2.30798E-4	5.48213E-4	0.421	0.67512
LT-TTG	Intercept	0.36559	0.01723	21.21201	3.53364E-31
	Slope	1.5291E-4	6.50491E-4	0.23507	0.81488

Fitted Curves Plot



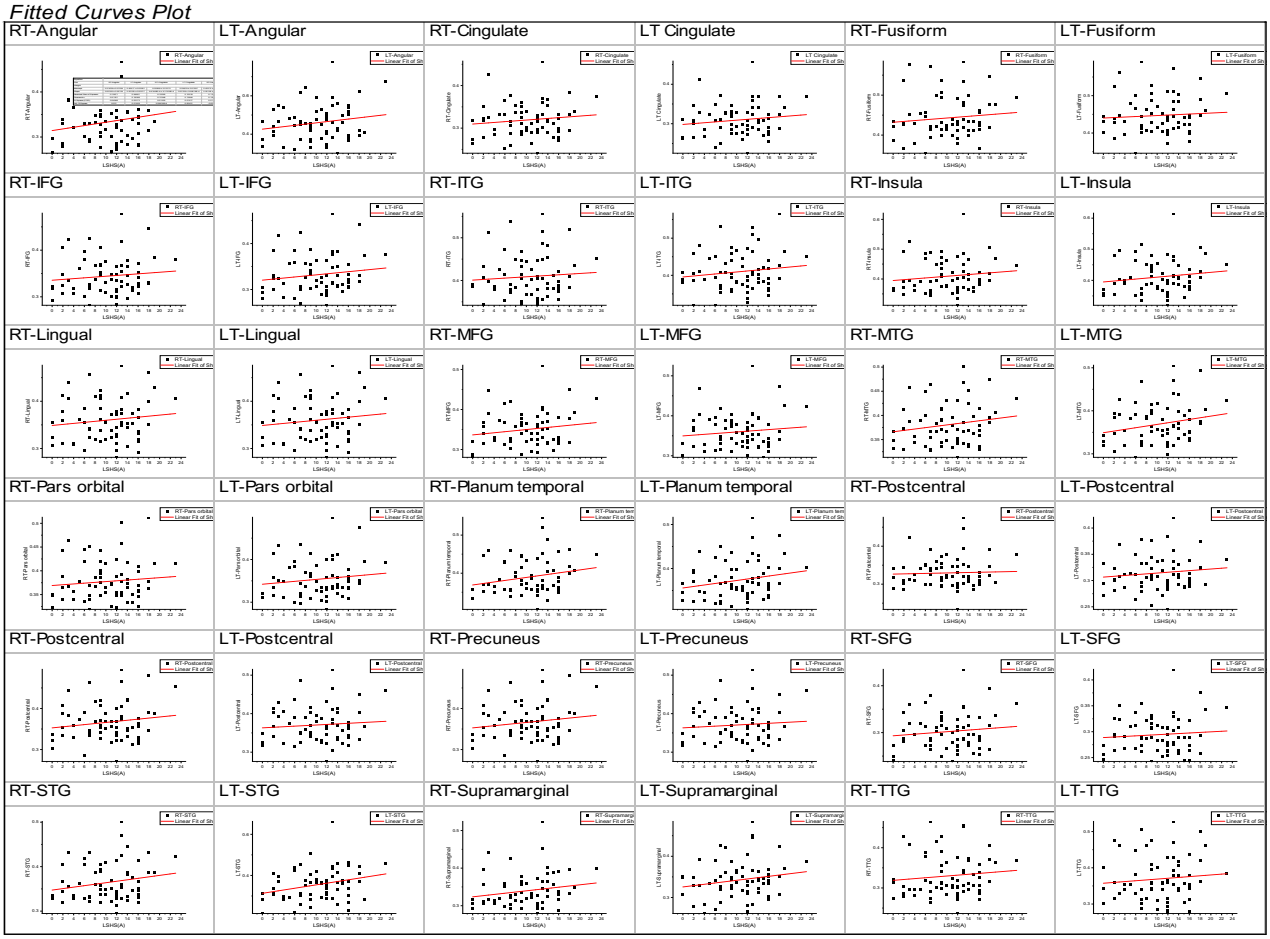
Residual Plots



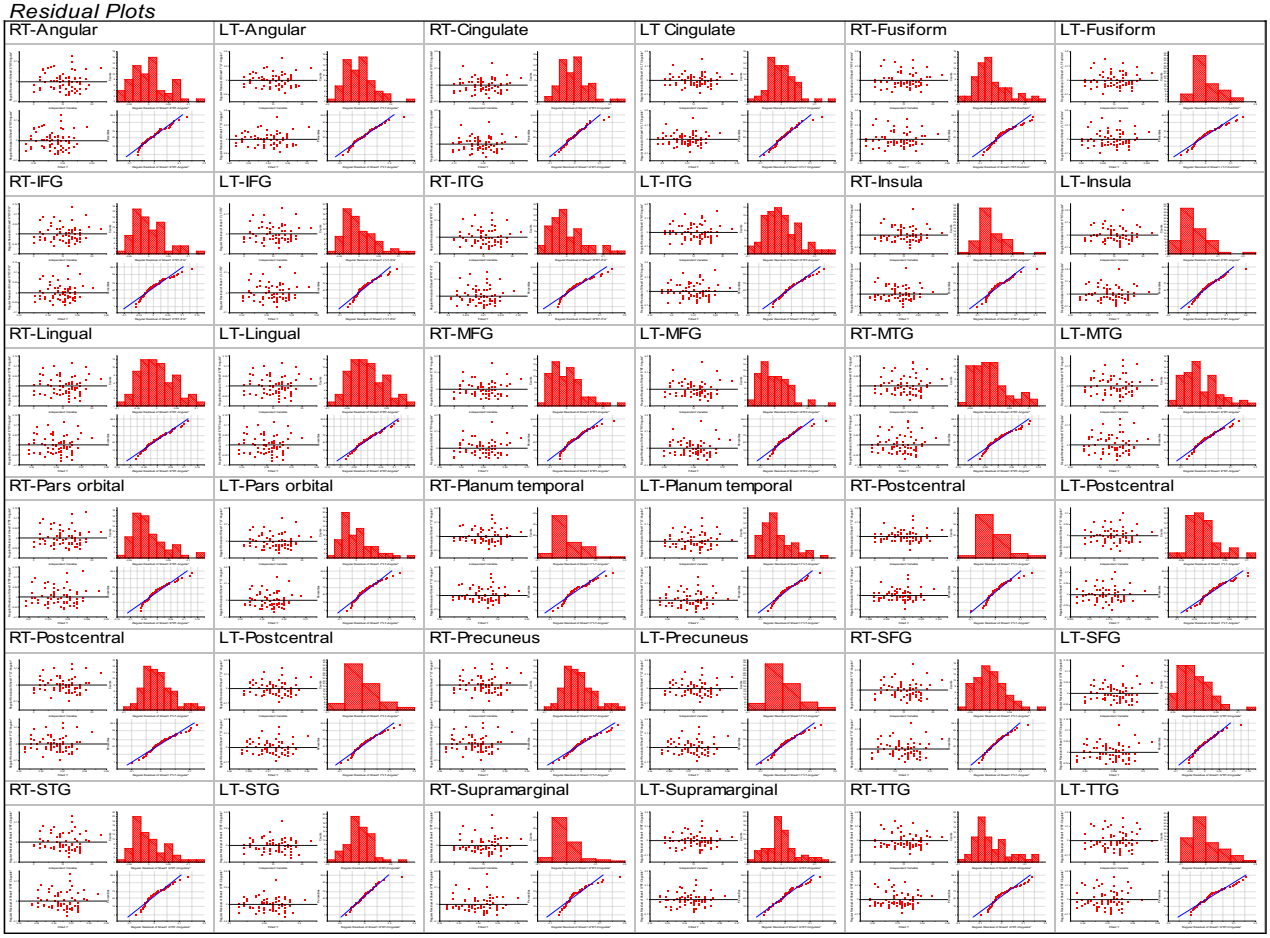
B2: CAT 12 result correlation with $LSHS_{(A)}$.

		Value	Standard Error	t-Value	Prob>|t|
RT-Angular	Intercept	0.31428	0.01204	26.10701	1.67606E-36
	Slope	0.00185	0.00104	1.77291	0.08086
LT-Angular	Intercept	0.42617	0.02501	17.04151	7.312E-26
	Slope	0.00329	0.00217	1.51786	0.13383
RT-Cingulate	Intercept	0.30958	0.01075	28.81075	4.21167E-39
	Slope	9.41448E-4	9.31309E-4	1.01089	0.31576
LT Cingulate	Intercept	0.29819	0.01097	27.1873	1.44391E-37
	Slope	0.00108	9.50618E-4	1.13565	0.26021
RT-Fusiform	Intercept	0.43212	0.01422	30.38763	1.5944E-40
	Slope	0.00106	0.00123	0.86241	0.39159
LT-Fusiform	Intercept	0.44014	0.01364	32.26125	3.92886E-42
	Slope	6.67712E-4	0.00118	0.56467	0.57421
RT-IFG	Intercept	0.33557	0.01087	30.85845	6.17238E-41
	Slope	8.55727E-4	9.42509E-4	0.90792	0.36722
LT-IFG	Intercept	0.3203	0.01099	29.13685	2.11356E-39
	Slope	0.00115	9.52796E-4	1.20987	0.23065
RT-ITG	Intercept	0.40082	0.0135	29.68079	6.79016E-40
	Slope	7.79933E-4	0.00117	0.66634	0.50752
LT-ITG	Intercept	0.39551	0.01398	28.29956	1.25813E-38
	Slope	0.00135	0.00121	1.11245	0.26998
RT-Insula	Intercept	0.39491	0.01499	26.34495	9.69783E-37
	Slope	0.00143	0.0013	1.09753	0.2764
LT-Insula	Intercept	0.3948	0.01453	27.17232	1.49301E-37
	Slope	0.00155	0.00126	1.2292	0.22336
RT-Lingual	Intercept	0.34876	0.01213	28.74112	4.88389E-39
	Slope	0.0011	0.00105	1.04309	0.30071
LT-Lingual	Intercept	0.34876	0.01213	28.74112	4.88389E-39
	Slope	0.0011	0.00105	1.04309	0.30071
RT-MFG	Intercept	0.33655	0.01174	28.67664	5.60326E-39
	Slope	0.00134	0.00102	1.31425	0.19331
LT-MFG	Intercept	0.34976	0.01201	29.11935	2.19284E-39
	Slope	9.89583E-4	0.00104	0.95056	0.34529
RT-MTG	Intercept	0.36613	0.01208	30.30032	1.90386E-40
	Slope	0.00142	0.00105	1.35894	0.17879
LT-MTG	Intercept	0.34909	0.01236	28.25146	1.39581E-38
	Slope	0.00193	0.00107	1.80224	0.07607
RT-Pars orbital	Intercept	0.36911	0.01183	31.19871	3.13322E-41
	Slope	8.25067E-4	0.00103	0.80461	0.42393
LT-Pars orbital	Intercept	0.34207	0.0115	29.7392	6.01719E-40
	Slope	0.00113	9.96935E-4	1.12873	0.2631
RT-Planum temporal	Intercept	0.36911	0.01283	28.77519	4.54232E-39
	Slope	0.00198	0.00111	1.78247	0.07927
LT-Planum temporal	Intercept	0.35566	0.01151	30.89494	5.73769E-41
	Slope	0.0017	9.97779E-4	1.70287	0.0933
RT-Postcentral	Intercept	0.32651	0.01082	30.16768	2.49484E-40
	Slope	3.02185E-4	9.38081E-4	0.32213	0.74837
LT-Postcentral	Intercept	0.30656	0.00946	32.42064	2.89243E-42
	Slope	7.6965E-4	8.19543E-4	0.93912	0.35109
RT-Postcentral	Intercept	0.35275	0.01227	28.76055	4.68606E-39
	Slope	0.00133	0.00106	1.2486	0.21622
LT-Postcentral	Intercept	0.36309	0.01241	29.25469	1.65012E-39
	Slope	7.40761E-4	0.00108	0.68861	0.49348
RT-Precuneus	Intercept	0.35275	0.01227	28.76055	4.68606E-39
	Slope	0.00133	0.00106	1.2486	0.21622
LT-Precuneus	Intercept	0.36309	0.01241	29.25469	1.65012E-39
	Slope	7.40761E-4	0.00108	0.68861	0.49348
RT-SFG	Intercept	0.29328	0.01039	28.22649	1.47321E-38
	Slope	8.69917E-4	9.00538E-4	0.966	0.33757
LT-SFG	Intercept	0.28868	0.00943	30.60521	1.02672E-40
	Slope	5.53636E-4	8.17526E-4	0.67721	0.50064
RT-STG	Intercept	0.34735	0.01135	30.59473	1.04865E-40
	Slope	0.00165	9.84024E-4	1.67803	0.09807
LT-STG	Intercept	0.31289	0.0203	15.41183	1.49472E-23
	Slope	0.00411	0.00176	2.3377	0.02244
RT-Supramargi nal	Intercept	0.3236	0.01199	26.99041	2.24355E-37
	Slope	0.0016	0.00104	1.54437	0.12728
LT-Supramargi nal	Intercept	0.32563	0.0123	26.47133	7.26413E-37
	Slope	0.00161	0.00107	1.5117	0.13538
RT-TTG	Intercept	0.3189	0.01395	22.85283	4.62296E-33
	Slope	0.00108	0.00121	0.89094	0.3762
LT-TTG	Intercept	0.35742	0.01656	21.57989	1.30792E-31
	Slope	0.00114	0.00144	0.79607	0.42885

Fitted Curves Plot



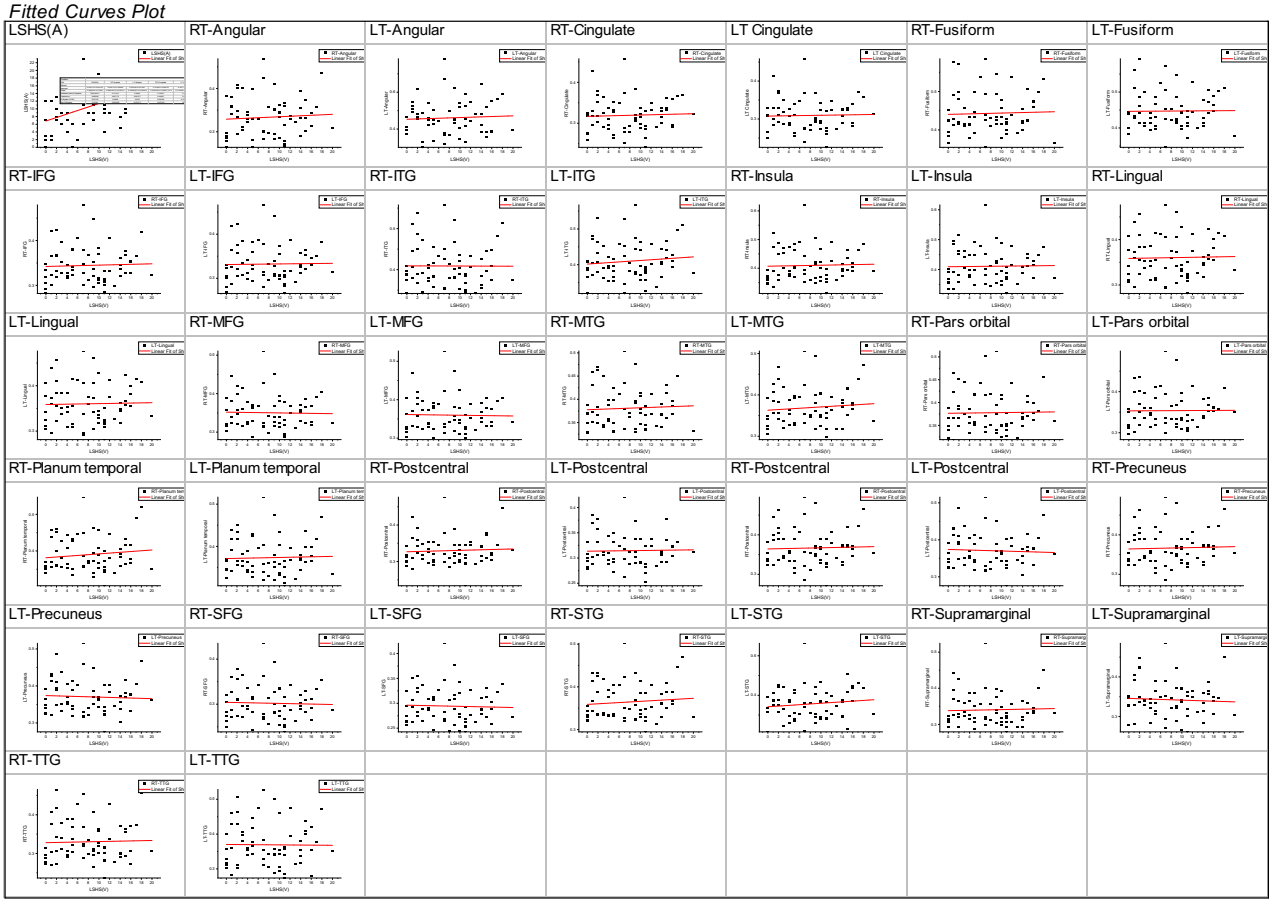
Residual Plots



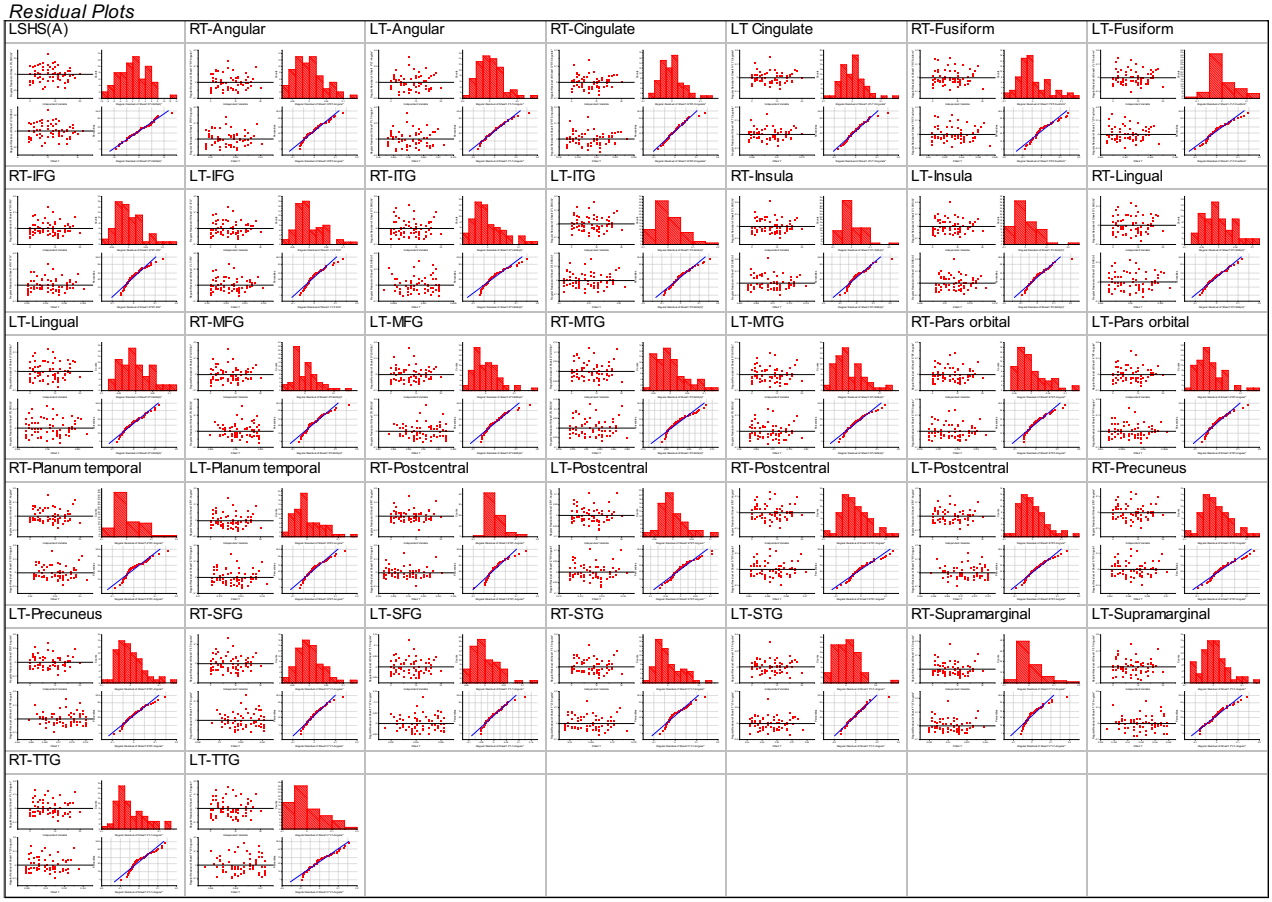
B3: CAT 12 result correlation with $LSHS_{(V)}$.

		Value	Standard Error	t-Value	Prob>|t|
LSHS(A)	Intercept	6.84123	0.96125	7.11702	1.00279E-9
	Slope	0.45659	0.10253	4.45326	3.34269E-5
RT-Angular	Intercept	0.32914	0.00949	34.68723	4.26725E-44
	Slope	5.58676E-4	0.00101	0.552	0.58281
LT-Angular	Intercept	0.45306	0.01961	23.107	2.41319E-33
	Slope	9.32005E-4	0.00209	0.44565	0.65731
RT-Cingulate	Intercept	0.31684	0.00835	37.94766	1.50107E-46
	Slope	3.22363E-4	8.90577E-4	0.36197	0.71853
LT Cingulate	Intercept	0.30774	0.00854	36.01553	4.03901E-45
	Slope	2.11592E-4	9.11388E-4	0.23216	0.81713
RT-Fusiform	Intercept	0.44047	0.01103	39.93168	5.96672E-48
	Slope	3.4506E-4	0.00118	0.29328	0.77023
LT-Fusiform	Intercept	0.44625	0.01056	42.2774	1.58568E-49
	Slope	1.04482E-4	0.00113	0.0928	0.92634
RT-IFG	Intercept	0.34215	0.00844	40.54407	2.27154E-48
	Slope	2.96352E-4	9.00112E-4	0.32924	0.74302
LT-IFG	Intercept	0.33116	0.00858	38.60989	5.02997E-47
	Slope	1.39355E-4	9.14868E-4	0.15232	0.8794
RT-ITG	Intercept	0.40925	0.01046	39.13109	2.15311E-47
	Slope	-4.6063E-5	0.00112	-0.04129	0.96719
LT-ITG	Intercept	0.40172	0.01083	37.10688	6.17003E-46
	Slope	0.00101	0.00115	0.87196	0.38639
RT-Insula	Intercept	0.407	0.01167	34.88039	3.01363E-44
	Slope	3.4749E-4	0.00124	0.2792	0.78096
LT-Insula	Intercept	0.4093	0.01134	36.09378	3.52393E-45
	Slope	1.9715E-4	0.00121	0.16299	0.87102
RT-Lingual	Intercept	0.35854	0.00944	37.98072	1.42074E-46
	Slope	2.04639E-4	0.00101	0.20323	0.83958
LT-Lingual	Intercept	0.35854	0.00944	37.98072	1.42074E-46
	Slope	2.04639E-4	0.00101	0.20323	0.83958
RT-MFG	Intercept	0.3519	0.00917	38.35962	7.5881E-47
	Slope	-1.95831E-4	9.7849E-4	-0.20014	0.84199
LT-MFG	Intercept	0.36146	0.00933	38.73465	4.10151E-47
	Slope	-1.89447E-4	9.95353E-4	-0.19033	0.84963
RT-MTG	Intercept	0.37763	0.00944	39.98753	5.46057E-48
	Slope	4.19371E-4	0.00101	0.41633	0.67852
LT-MTG	Intercept	0.36299	0.00973	37.31907	4.30697E-46
	Slope	7.9035E-4	0.00104	0.7618	0.44889
RT-Pars orbital	Intercept	0.37649	0.00917	41.03484	1.05781E-48
	Slope	1.50939E-4	9.78624E-4	0.15424	0.87789
LT-Pars orbital	Intercept	0.35321	0.00896	39.40636	1.38123E-47
	Slope	6.67181E-5	9.56037E-4	0.06979	0.94457
RT-Planum temporal	Intercept	0.38143	0.01006	37.90953	1.59944E-46
	Slope	0.00107	0.00107	0.99248	0.32459
LT-Planum temporal	Intercept	0.37125	0.00907	40.91459	1.27467E-48
	Slope	2.60086E-4	9.67845E-4	0.26873	0.78898
RT-Postcentral	Intercept	0.32665	0.00835	39.1262	2.17023E-47
	Slope	3.89081E-4	8.90484E-4	0.43693	0.66359
LT-Postcentral	Intercept	0.31349	0.00735	42.67885	8.68449E-50
	Slope	1.3401E-4	7.83483E-4	0.17104	0.86471
RT-Postcentral	Intercept	0.36424	0.00957	38.05193	1.26222E-46
	Slope	2.92833E-4	0.00102	0.28681	0.77516
LT-Postcentral	Intercept	0.37397	0.0096	38.94565	2.90843E-47
	Slope	-4.16694E-4	0.00102	-0.40685	0.68544
RT-Precuneus	Intercept	0.36424	0.00957	38.05193	1.26222E-46
	Slope	2.92833E-4	0.00102	0.28681	0.77516
LT-Precuneus	Intercept	0.37397	0.0096	38.94565	2.90843E-47
	Slope	-4.16694E-4	0.00102	-0.40685	0.68544
RT-SFG	Intercept	0.30415	0.00807	37.68311	2.3346E-46
	Slope	-2.4337E-4	8.60914E-4	-0.28269	0.7783
LT-SFG	Intercept	0.29621	0.0073	40.57339	2.16966E-48
	Slope	-2.34628E-4	7.78715E-4	-0.3013	0.76413
RT-STG	Intercept	0.35895	0.00891	40.28582	3.40781E-48
	Slope	7.14238E-4	9.50384E-4	0.75153	0.45501
LT-STG	Intercept	0.34173	0.01618	21.12676	4.45707E-31
	Slope	0.00179	0.00173	1.03592	0.30402
RT-Supramarginal	Intercept	0.33798	0.00941	35.90209	4.92468E-45
	Slope	2.90291E-4	0.001	0.2891	0.77341
LT-Supramarginal	Intercept	0.34572	0.00964	35.84701	5.42337E-45
	Slope	-4.42682E-4	0.00103	-0.43033	0.66836
RT-TTG	Intercept	0.32788	0.01083	30.27294	2.01297E-40
	Slope	2.83583E-4	0.00116	0.24548	0.80685
LT-TTG	Intercept	0.37018	0.01284	28.81962	4.133E-39
	Slope	-1.20331E-4	0.00137	-0.08783	0.93028

Fitted Curves Plot



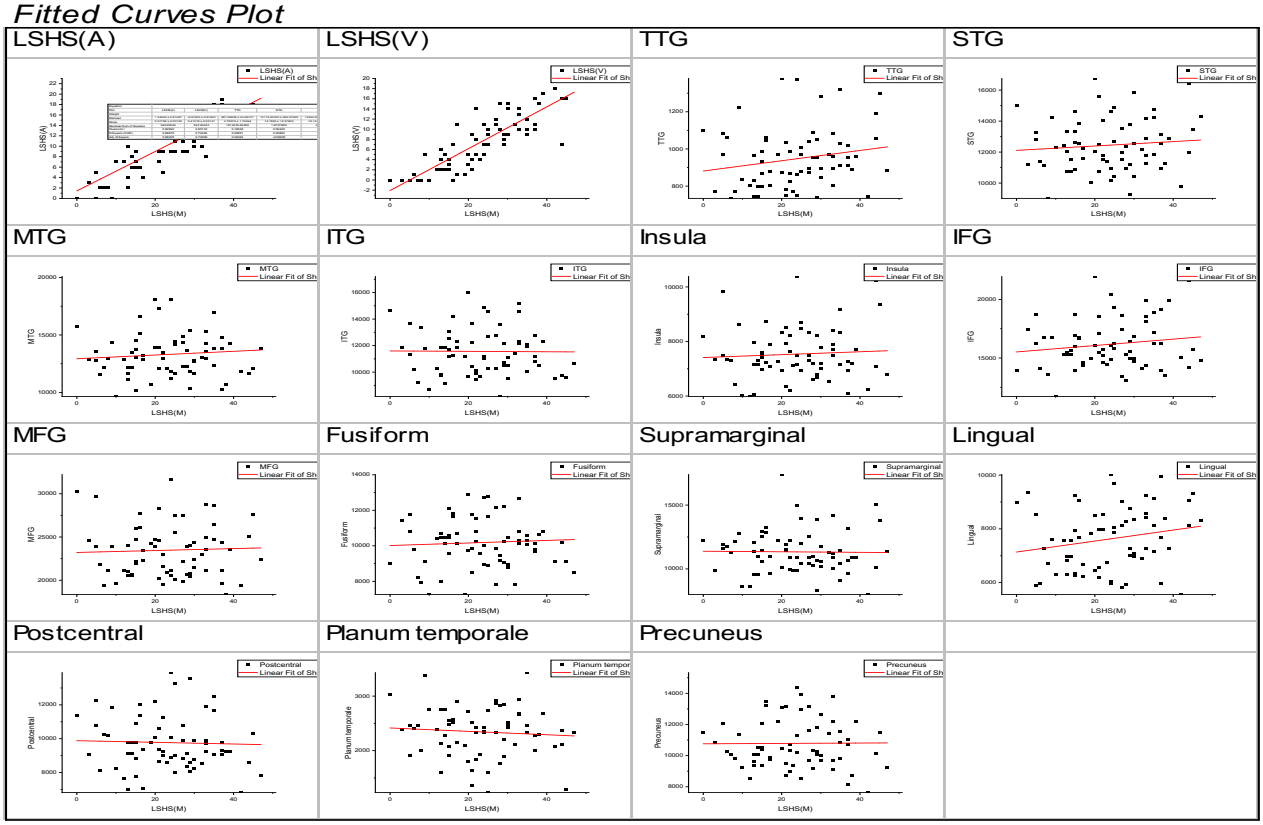
Residual Plots



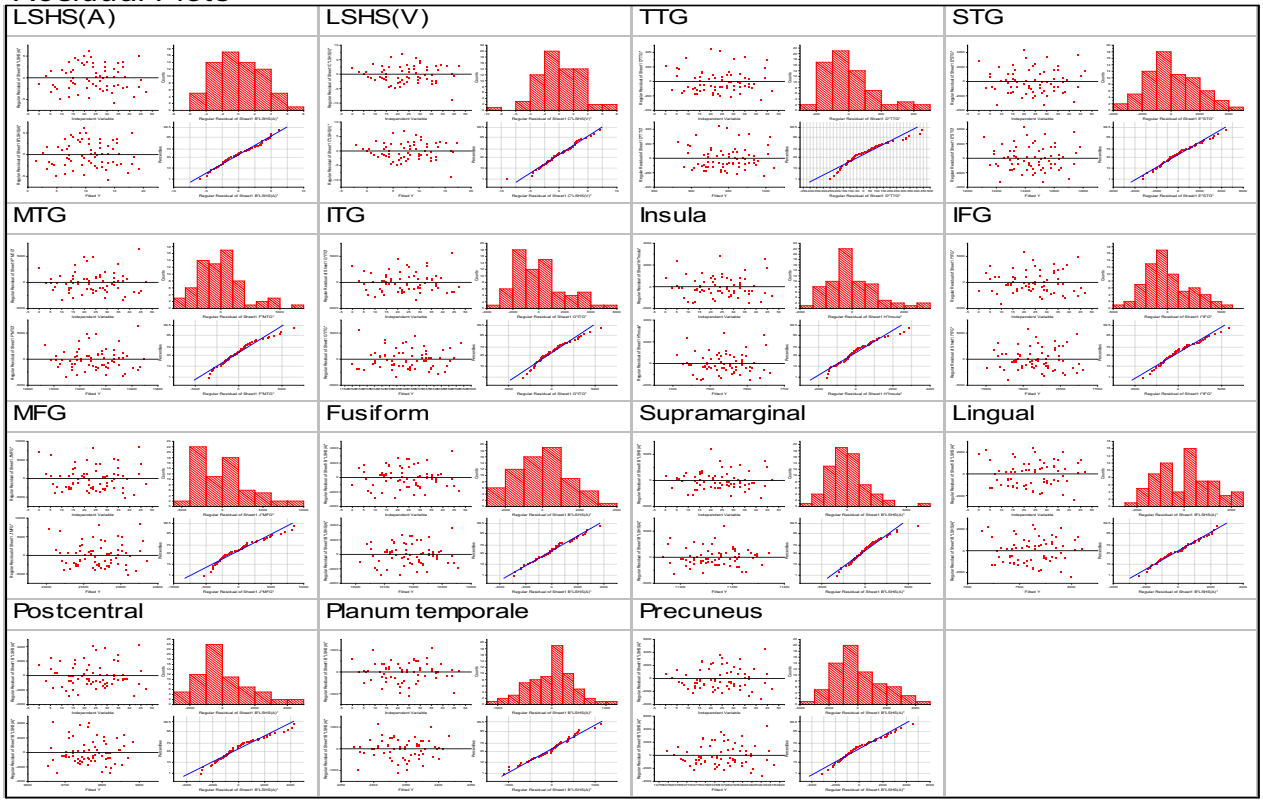
B4-1: FreeSurfer Correlation results for right hemisphere volumes with $LSHS_{(M)}$.

		Value	Standard Error	t-Value	Prob>|t|
LSHS(A)	Intercept	1.44622	0.81687	1.77045	0.08127
	Slope	0.37766	0.03125	12.08537	2.19137E-18
LSHS(V)	Intercept	-2.07655	0.81834	-2.53752	0.01353
	Slope	0.41218	0.03131	13.16639	3.93366E-20
TTG	Intercept	881.36608	44.56737	19.77604	1.94155E-29
	Slope	2.76079	1.70494	1.61929	0.11015
STG	Intercept	12110.40332	480.37626	25.21025	1.36833E-35
	Slope	14.1663	18.37693	0.77087	0.44353
MTG	Intercept	12932.55286	565.98466	22.84965	4.66082E-33
	Slope	16.14444	21.65191	0.74564	0.45853
ITG	Intercept	11598.2102	528.82005	21.93224	5.10887E-32
	Slope	-1.55767	20.23016	-0.077	0.93886
Insula	Intercept	7411.19032	270.27369	27.42106	8.58643E-38
	Slope	5.31079	10.3394	0.51365	0.60922
IFG	Intercept	15517.28235	590.01469	26.29982	1.07547E-36
	Slope	27.35973	22.57118	1.21215	0.22978
MFG	Intercept	23215.0417	911.4102	25.47156	7.37487E-36
	Slope	11.15237	34.86626	0.31986	0.75008
Fusiform	Intercept	10016.78338	407.20037	24.59915	5.92766E-35
	Slope	7.18691	15.57757	0.46136	0.64606
Supramarginal	Intercept	11384.79073	479.69365	23.73346	4.97732E-34
	Slope	-2.15834	18.35082	-0.11762	0.90673
Lingual	Intercept	7137.22121	327.24877	21.80977	7.07385E-32
	Slope	20.44746	12.519	1.63331	0.10716
Postcentral	Intercept	9883.31836	466.70635	21.17674	3.88961E-31
	Slope	-4.90593	17.85399	-0.27478	0.78434
Planum temporale	Intercept	2415.93633	127.3109	18.97667	1.97927E-28
	Slope	-3.11167	4.87032	-0.6389	0.5251
Precuneus	Intercept	10759.23523	465.16238	23.13006	2.27557E-33
	Slope	1.2225	17.79492	0.0687	0.94544

Fitted Curves Plot



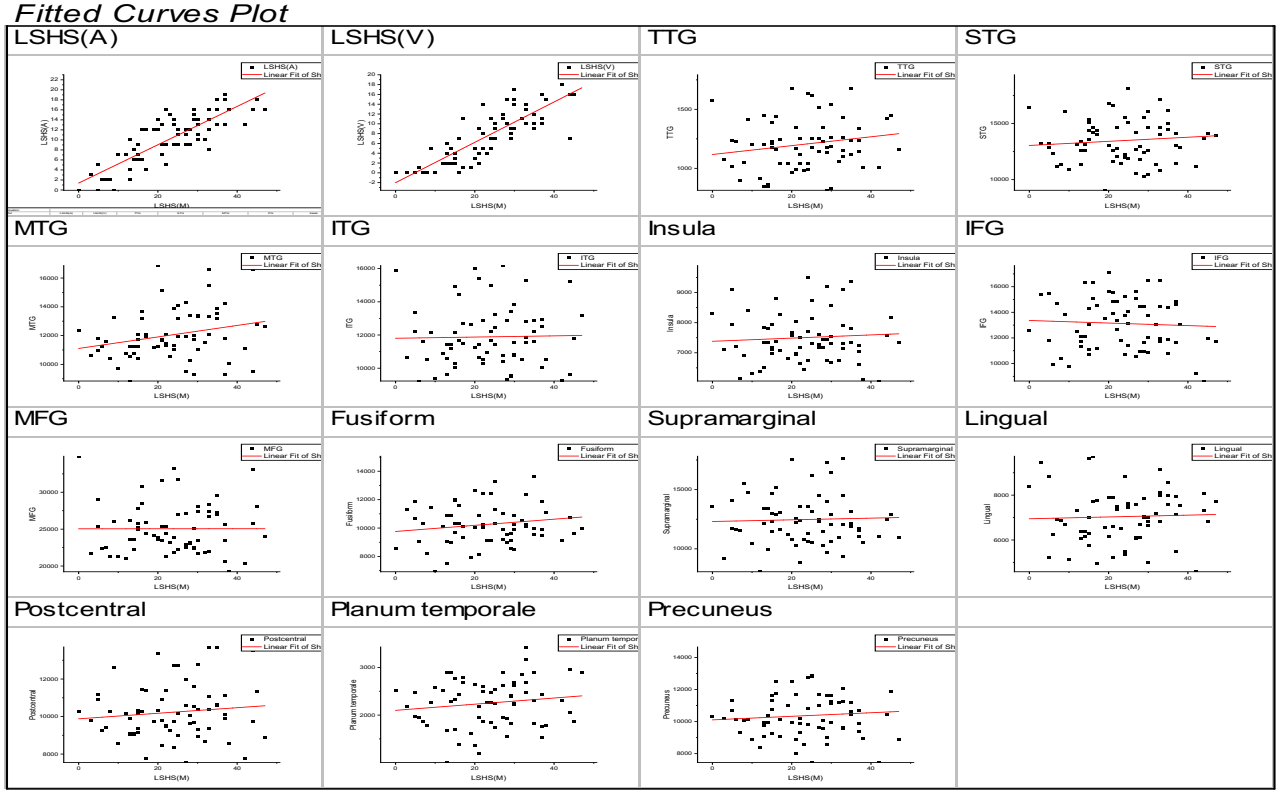
Residual Plots



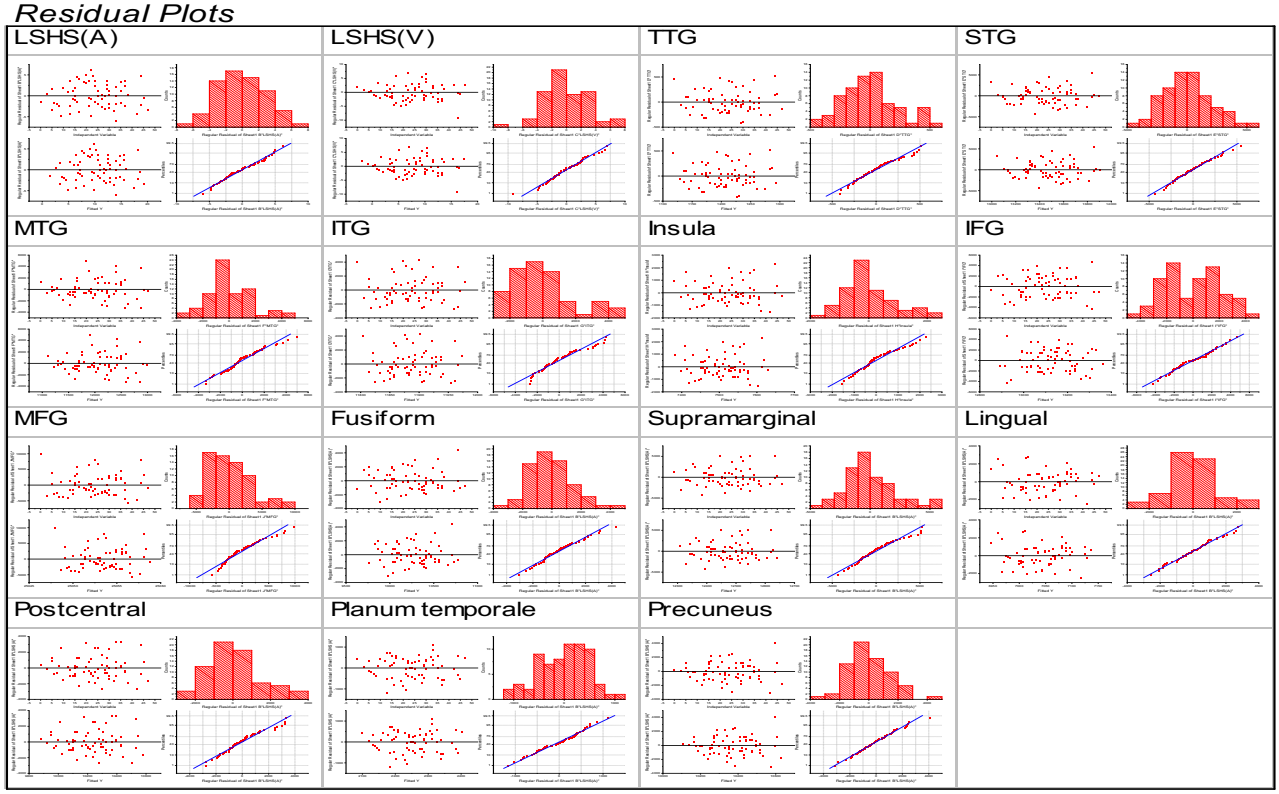
B4-2: FreeSurfer Correlation results for left hemisphere volumes with $LSHS_{(M)}$.

		Value	Standard Error	t-Value	Prob>|t|
LSHS(A)	Intercept	1.37688	0.8183	1.68262	0.09718
	Slope	0.38273	0.03152	12.14422	1.75403E-18
LSHS(V)	Intercept	-2.01336	0.84923	-2.3708	0.02068
	Slope	0.41182	0.03271	12.59114	3.28057E-19
TTG	Intercept	1117.42349	63.13117	17.70003	9.32295E-27
	Slope	3.75263	2.4314	1.5434	0.12752
STG	Intercept	13046.07087	572.84207	22.77429	5.6579E-33
	Slope	18.31949	22.06216	0.83036	0.40933
MTG	Intercept	11106.78127	487.36489	22.78946	5.44118E-33
	Slope	39.9593	18.77014	2.12888	0.037
ITG	Intercept	11803.38808	515.51526	22.89629	4.13492E-33
	Slope	3.60726	19.85431	0.18169	0.85639
Insula	Intercept	7381.47698	243.0778	30.36673	1.66351E-40
	Slope	5.29598	9.36178	0.5657	0.57351
IFG	Intercept	13361.65346	597.20747	22.37355	1.59959E-32
	Slope	-9.9534	23.00056	-0.43275	0.66661
MFG	Intercept	25047.95541	959.9173	26.09387	1.7277E-36
	Slope	0.23127	36.96979	0.00626	0.99503
Fusiform	Intercept	9759.99142	416.59076	23.42825	1.06958E-33
	Slope	21.60286	16.04438	1.34644	0.18277
Supramarginal	Intercept	12307.93571	612.89957	20.08149	8.13785E-30
	Slope	7.07898	23.60492	0.29989	0.7652
Lingual	Intercept	6946.67794	332.33784	20.90246	8.23762E-31
	Slope	4.05181	12.7995	0.31656	0.75258
Postcentral	Intercept	9877.99877	410.49943	24.06337	2.19632E-34
	Slope	14.84255	15.80978	0.93882	0.35125
Planum temporale	Intercept	2099.20439	140.40596	14.95096	7.14221E-23
	Slope	6.46756	5.40753	1.19603	0.23596
Precuneus	Intercept	10106.91396	391.02042	25.84754	3.0582E-36
	Slope	11.13491	15.05957	0.73939	0.46229

Fitted Curves Plot



Residual Plots

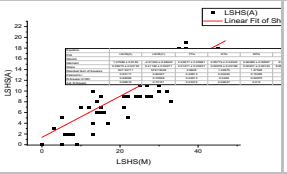


B4-3: FreeSurfer Correlation results for right hemisphere thickness with $LSHS_{(M)}$.

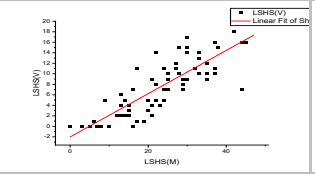
		Value	Standard Error	t-Value	Prob>|t|
LSHS(A)	Intercept	1.37688	0.8183	1.68262	0.09718
	Slope	0.38273	0.03152	12.14422	1.75403E-18
LSHS(V)	Intercept	-2.01336	0.84923	-2.3708	0.02068
	Slope	0.41182	0.03271	12.59114	3.28057E-19
TTG	Intercept	2.24817	0.05991	37.52441	3.04692E-46
	Slope	0.01071	0.00231	4.64218	1.68916E-5
STG	Intercept	2.85719	0.04323	66.09075	4.94407E-62
	Slope	0.00279	0.00166	1.67764	0.09815
MTG	Intercept	2.96486	0.03987	74.37244	2.2611E-65
	Slope	0.00207	0.00154	1.34687	0.18263
ITG	Intercept	2.87175	0.03027	94.87666	2.7475E-72
	Slope	8.66751E-4	0.00117	0.74352	0.4598
Insula	Intercept	3.12638	0.04929	63.43356	7.11834E-61
	Slope	0.00241	0.0019	1.27163	0.20797
IFG	Intercept	2.62167	0.04004	65.47036	9.12906E-62
	Slope	0.00129	0.00154	0.83877	0.40463
MFG	Intercept	2.82262	0.03429	82.31866	2.98615E-68
	Slope	0.00135	0.00132	1.01927	0.3118
Fusiform	Intercept	2.79715	0.03241	86.31597	1.3435E-69
	Slope	0.00202	0.00125	1.62053	0.10989
Supramarginal	Intercept	2.69472	0.03743	72.00311	1.86739E-64
	Slope	0.00104	0.00144	0.72185	0.47293
Lingual	Intercept	2.10451	0.03013	69.85257	1.34686E-63
	Slope	0.00159	0.00116	1.37276	0.17447
Postcentral	Intercept	2.13553	0.03782	56.46712	1.34105E-57
	Slope	0.00108	0.00146	0.74014	0.46184
Planum temporale	Intercept	3.49015	0.12436	28.06459	2.0924E-38
	Slope	1.37519E-4	0.00479	0.02871	0.97718
Precuneus	Intercept	2.46574	0.03032	81.31674	6.64915E-68
	Slope	0.00191	0.00117	1.63743	0.1063

Fitted Curves Plot

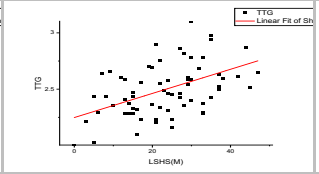
LSHS(A)



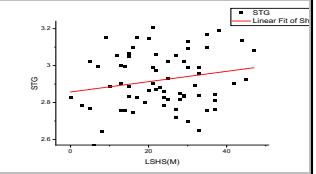
LSHS(V)



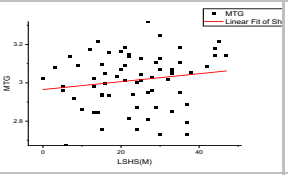
TTG



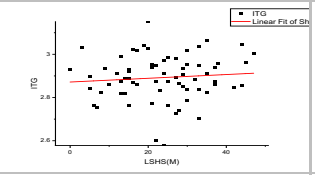
STG



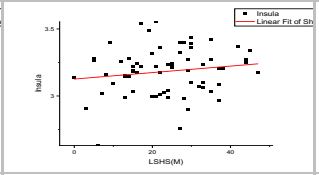
MTG



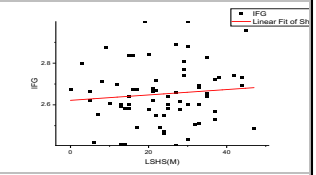
ITG



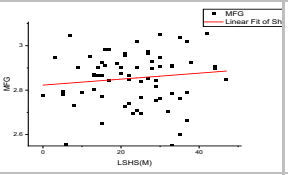
Insula



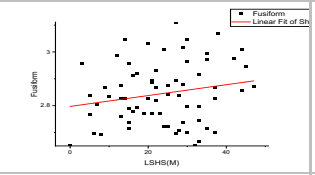
IFG



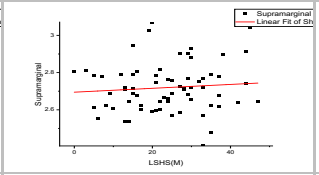
MFG



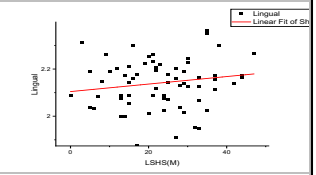
Fusiform



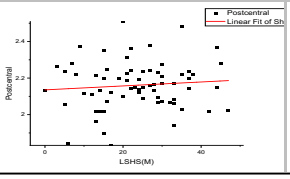
Supramarginal



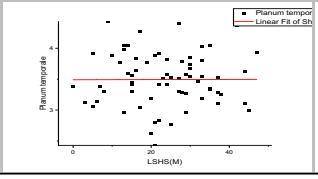
Lingual



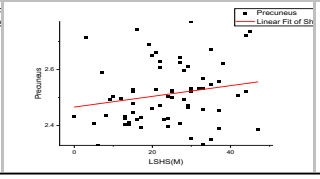
Postcentral



Planum temporale

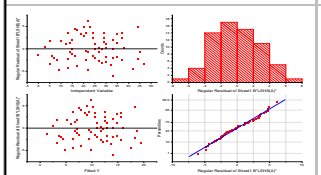


Precuneus

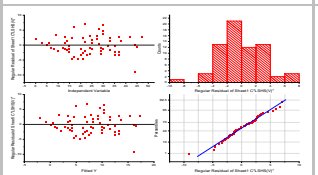


Residual Plots

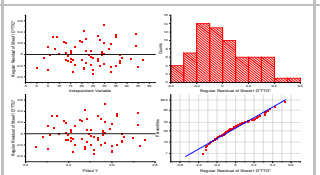
LSHS(A)



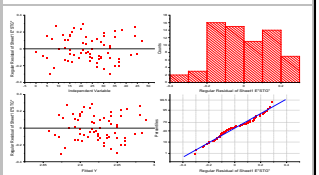
LSHS(V)



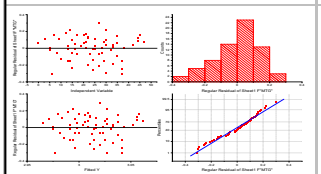
TTG



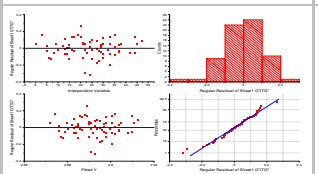
STG



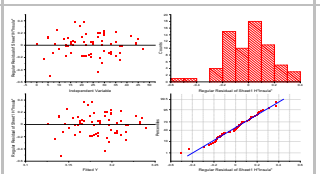
MTG



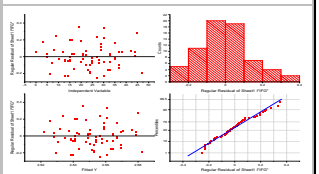
ITG



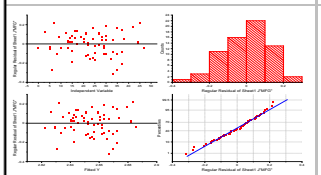
Insula



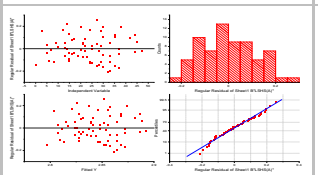
IFG



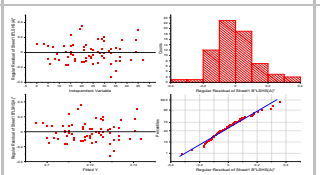
MFG



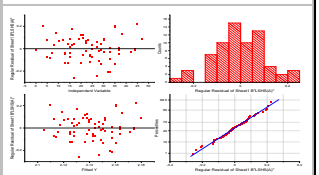
Fusiform



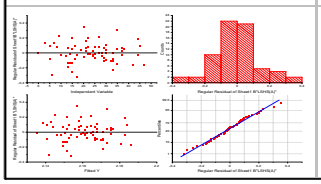
Supramarginal



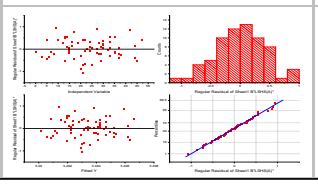
Lingual



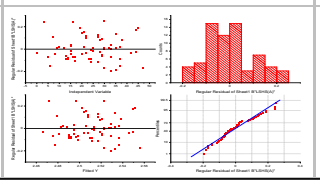
Postcentral



Planum temporale



Precuneus

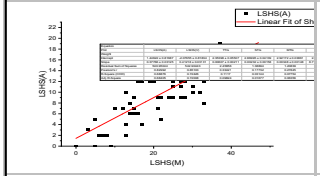


B4-4: FreeSurfer Correlation results for left hemisphere thickness with $LSHS_{(M)}$.

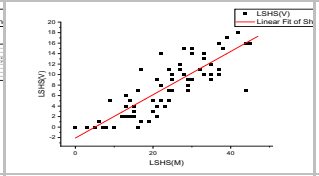
		Value	Standard Error	t-Value	Prob>|t|
LSHS(A)	Intercept	1.44622	0.81687	1.77045	0.08127
	Slope	0.37766	0.03125	12.08537	2.19137E-18
LSHS(V)	Intercept	-2.07655	0.81834	-2.53752	0.01353
	Slope	0.41218	0.03131	13.16639	3.93366E-20
TTG	Intercept	2.35398	0.05507	42.74559	7.86123E-50
	Slope	0.00607	0.00211	2.88081	0.00535
STG	Intercept	2.86995	0.04139	69.33632	2.18343E-63
	Slope	0.00232	0.00158	1.46372	0.14802
MTG	Intercept	2.92172	0.03861	75.67668	7.27254E-66
	Slope	0.00348	0.00148	2.35533	0.02149
ITG	Intercept	2.86167	0.03293	86.89303	8.6871E-70
	Slope	8.77631E-4	0.00126	0.6966	0.4885
Insula	Intercept	3.0565	0.03858	79.22563	3.64823E-67
	Slope	0.00235	0.00148	1.58979	0.11666
IFG	Intercept	2.52919	0.03769	67.09728	1.84965E-62
	Slope	0.00153	0.00144	1.06432	0.29106
MFG	Intercept	2.25373	0.03232	69.73983	1.49629E-63
	Slope	0.00153	0.00124	1.23737	0.22033
Fusiform	Intercept	2.74991	0.03055	90.02695	8.5429E-71
	Slope	0.00254	0.00117	2.1721	0.03345
Supramarginal	Intercept	2.64829	0.03393	78.05212	9.6694E-67
	Slope	0.00228	0.0013	1.75921	0.08318
Lingual	Intercept	2.1019	0.03128	67.20339	1.66894E-62
	Slope	2.70945E-4	0.0012	0.22645	0.82155
Postcentral	Intercept	2.15497	0.03349	64.34309	2.82293E-61
	Slope	0.00171	0.00128	1.33778	0.18556
Planum temporale	Intercept	3.07377	0.11014	27.90709	2.94853E-38
	Slope	0.00937	0.00421	2.22428	0.02956
Precuneus	Intercept	2.45949	0.03353	73.35394	5.55812E-65
	Slope	0.00144	0.00128	1.12005	0.26675

Fitted Curves Plot

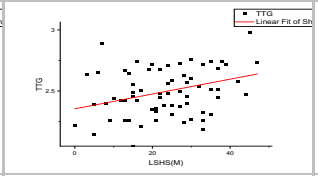
LSHS(A)



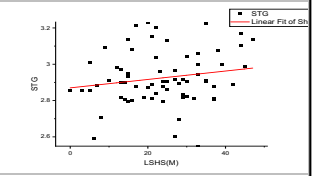
LSHS(V)



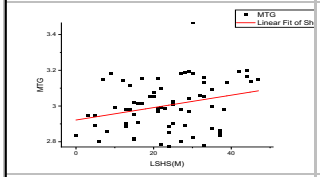
TTG



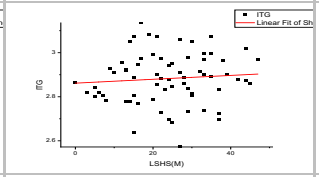
STG



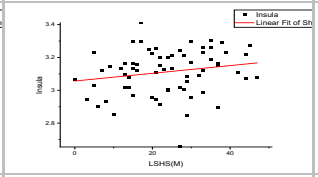
MTG



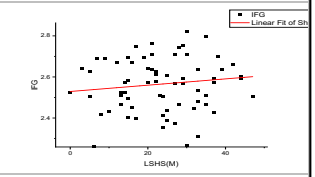
ITG



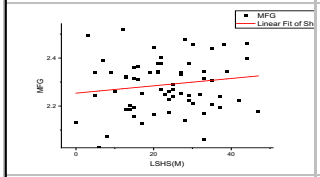
Insula



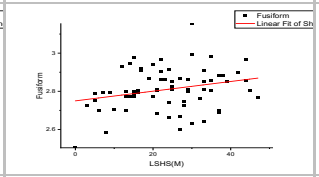
IFG



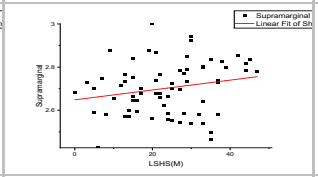
MFG



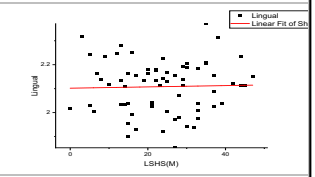
Fusiform



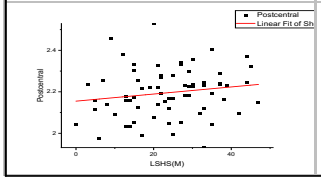
Supramarginal



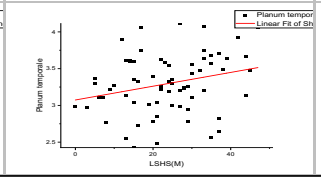
Lingual



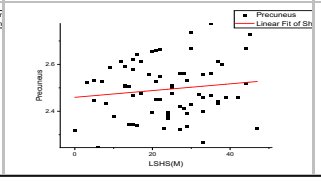
Postcentral



Planum temporale

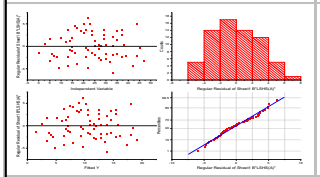


Precuneus

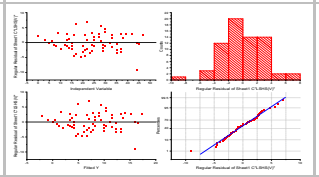


Residual Plots

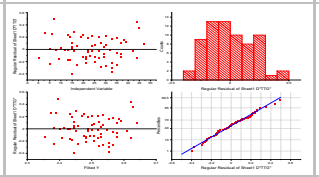
LSHS(A)



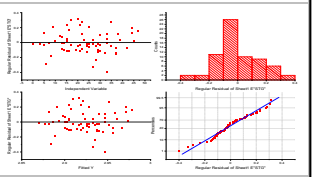
LSHS(V)



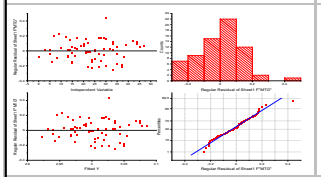
TTG



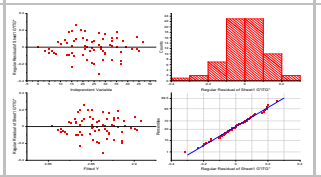
STG



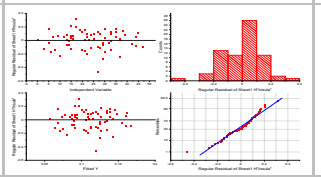
MTG



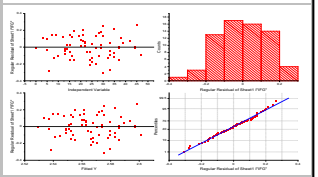
ITG



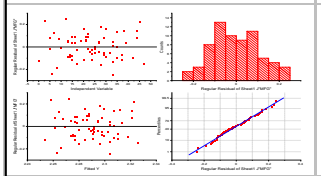
Insula



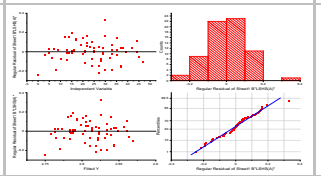
IFG



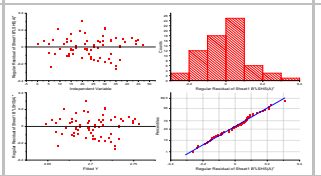
MFG



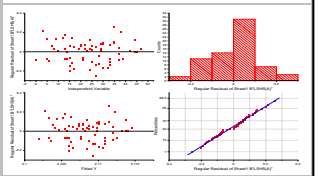
Fusiform



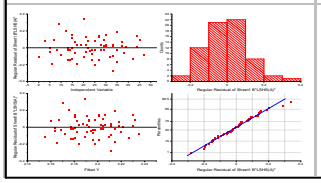
Supramarginal



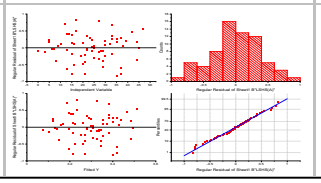
Lingual



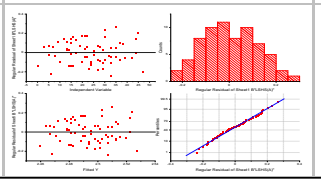
Postcentral



Planum temporale



Precuneus

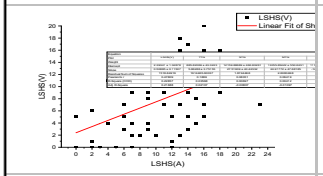


B5-1: FreeSurfer Correlation results for right hemisphere volume with $LSHS_{(A)}$.

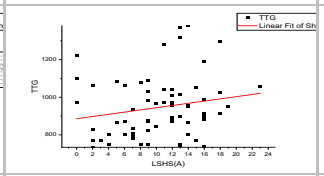
		Value	Standard Error	t-Value	Prob>|t|
LSHS(V)	Intercept	2.39341	1.32878	1.8012	0.07624
	Slope	0.50885	0.11507	4.42219	3.73521E-5
TTG	Intercept	885.82069	43.3223	20.44722	2.90915E-30
	Slope	5.86288	3.75155	1.56279	0.12288
STG	Intercept	12159.88689	466.80261	26.04931	1.91506E-36
	Slope	27.51939	40.42332	0.68078	0.49839
MTG	Intercept	13055.85422	550.6231	23.71105	5.26345E-34
	Slope	24.91772	47.68185	0.52258	0.60301
ITG	Intercept	11714.605	512.96685	22.83696	4.8153E-33
	Slope	-14.76082	44.42097	-0.33229	0.74072
Insula	Intercept	7463.14059	262.70887	28.40841	9.95222E-39
	Slope	7.09977	22.74958	0.31208	0.75596
IFG	Intercept	15592.41041	573.79636	27.17412	1.48703E-37
	Slope	55.11769	49.68857	1.10926	0.27134
MFG	Intercept	23069.10077	883.69307	26.10533	1.68257E-36
	Slope	39.4733	76.52444	0.51583	0.6077
Fusiform	Intercept	9818.22219	392.71314	25.001	2.25308E-35
	Slope	35.5041	34.00746	1.04401	0.30029
Supramarginal	Intercept	11273.98964	465.65834	24.21086	1.52793E-34
	Slope	5.75312	40.32423	0.14267	0.88698
Lingual	Intercept	7186.48237	318.53784	22.56084	9.824E-33
	Slope	41.85581	27.58416	1.51739	0.13394
Postcentral	Intercept	9526.96852	452.13747	21.07096	5.19064E-31
	Slope	23.14184	39.15337	0.59106	0.5565
Planum temporale	Intercept	2485.67978	122.40984	20.30621	4.31838E-30
	Slope	-13.8091	10.60022	-1.30272	0.1972
Precuneus	Intercept	10679.15795	451.34403	23.66079	5.96739E-34
	Slope	10.49895	39.08467	0.26862	0.78906

Fitted Curves Plot

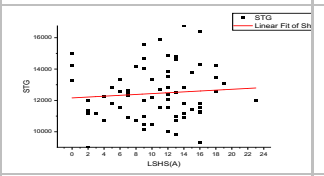
LSHS(V)



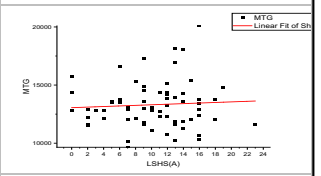
TTG



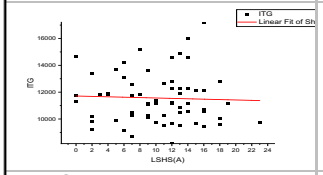
STG



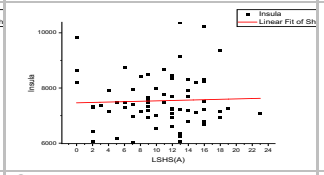
MTG



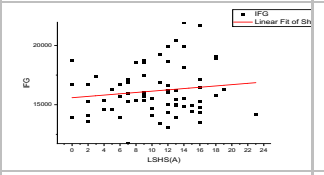
ITG



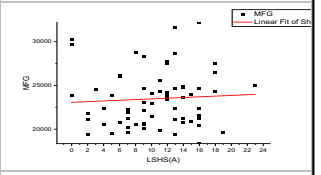
Insula



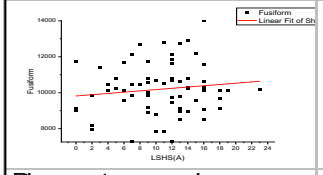
IFG



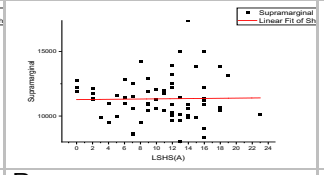
MFG



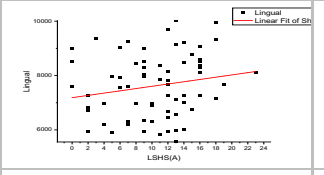
Fusiform



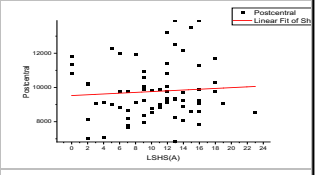
Supramarginal



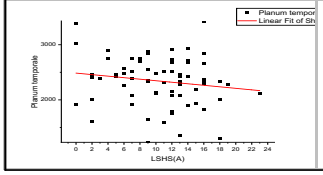
Lingual



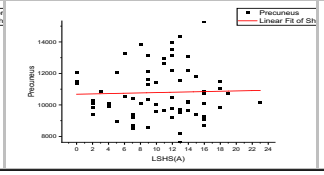
Postcentral



Planum temporale

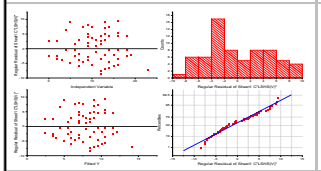


Precuneus

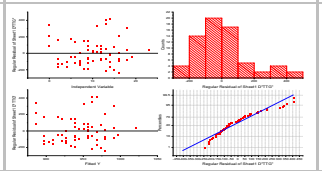


Residual Plots

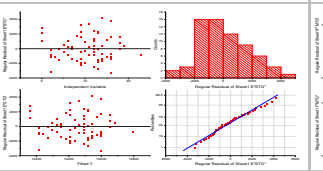
LSHS(V)



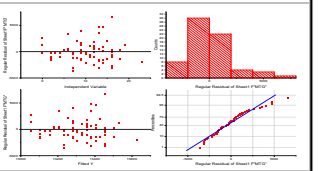
TTG



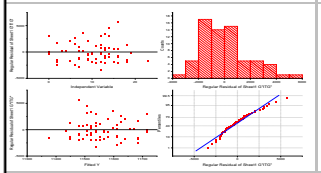
STG



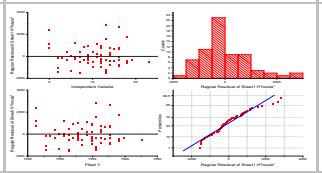
MTG



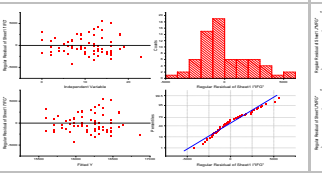
ITG



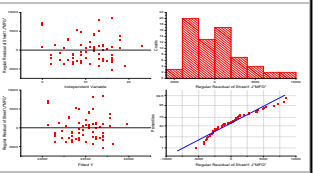
Insula



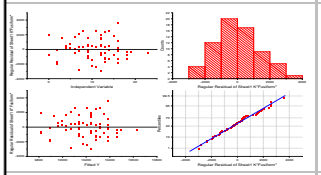
IFG



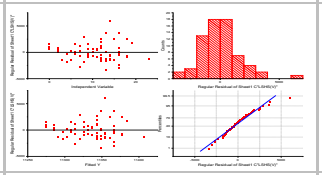
MFG



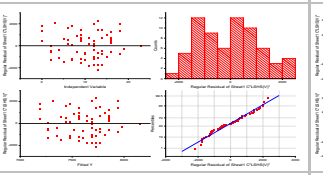
Fusiform



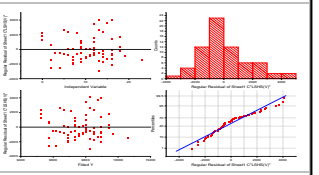
Supramarginal



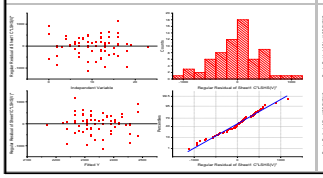
Lingual



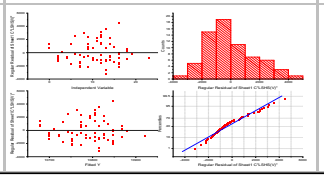
Postcentral



Planum temporale



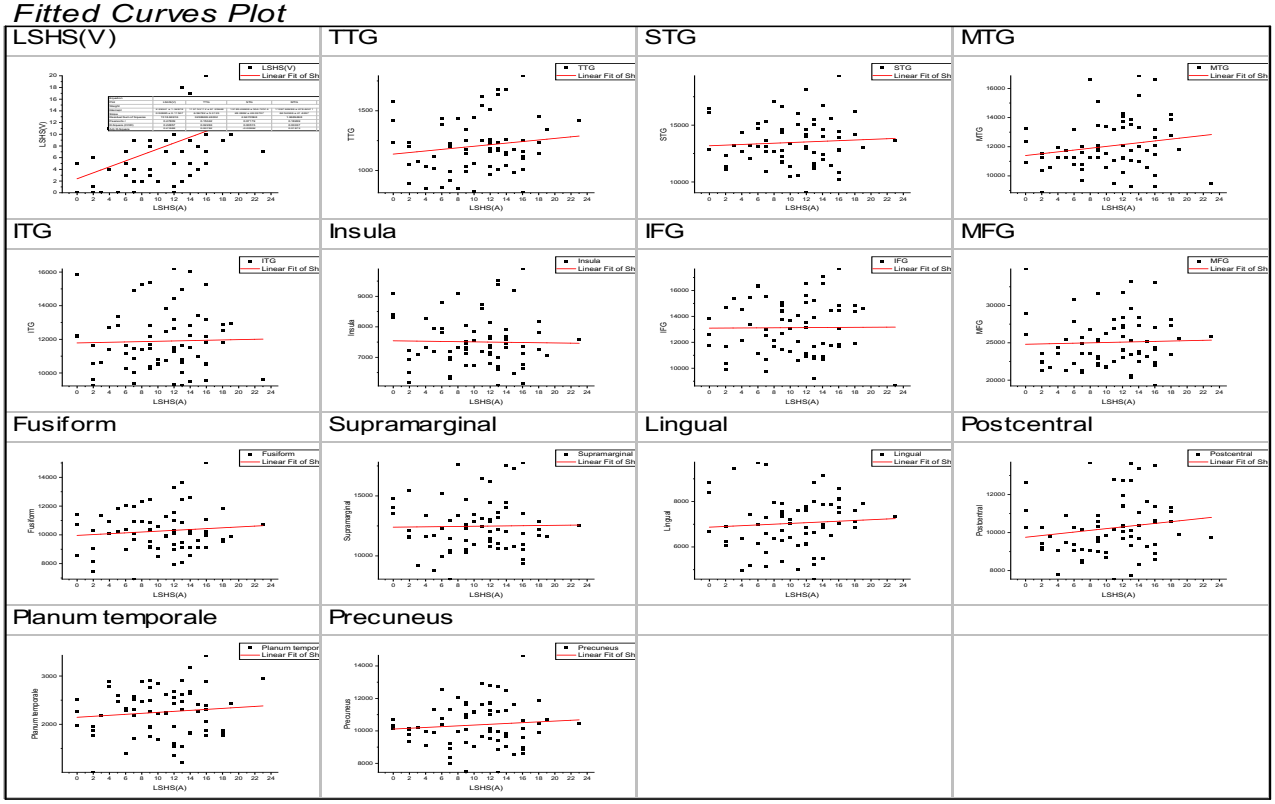
Precuneus



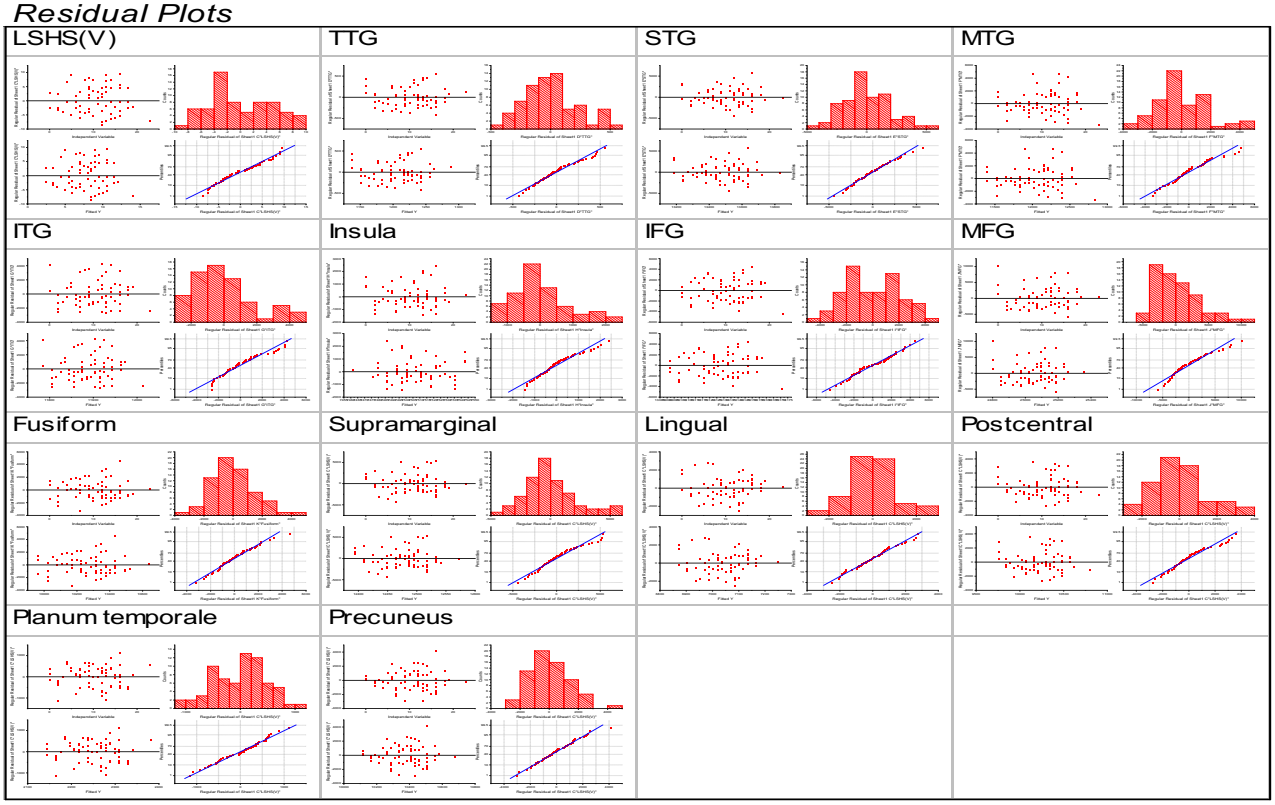
B5-2: FreeSurfer Correlation results for left hemisphere volume with $LSHS_{(A)}$.

		Value	Standard Error	t-Value	Prob>|t|
LSHS(V)	Intercept	2.39341	1.32878	1.8012	0.07624
	Slope	0.50885	0.11507	4.42219	3.73521E-5
TTG	Intercept	1137.53112	61.35948	18.5388	7.26896E-28
	Slope	6.56782	5.3135	1.23606	0.22082
STG	Intercept	13185.49606	554.72514	23.76942	4.55069E-34
	Slope	28.0882	48.03707	0.58472	0.56073
MTG	Intercept	11397.68286	478.42411	23.82339	3.97888E-34
	Slope	62.54046	41.4297	1.50956	0.13593
ITG	Intercept	11785.75219	497.83539	23.67399	5.77375E-34
	Slope	9.87373	43.11064	0.22903	0.81955
Insula	Intercept	7542.427	235.29179	32.05563	5.8439E-42
	Slope	-3.50005	20.37537	-0.17178	0.86414
IFG	Intercept	13091.75717	577.60791	22.66547	7.49207E-33
	Slope	3.4384	50.01863	0.06874	0.9454
MFG	Intercept	24802.88691	926.4986	26.77056	3.68162E-37
	Slope	24.12846	80.23123	0.30074	0.76456
Fusiform	Intercept	9962.74576	405.70048	24.5569	6.56713E-35
	Slope	29.42959	35.13211	0.83768	0.40523
Supramarginal	Intercept	12394.65178	592.26931	20.92739	7.69211E-31
	Slope	7.69076	51.28826	0.14995	0.88126
Lingual	Intercept	6871.71752	320.38374	21.4484	1.86304E-31
	Slope	16.40256	27.74401	0.59121	0.5564
Postcentral	Intercept	9755.11776	393.84927	24.76866	3.93553E-35
	Slope	45.47308	34.10584	1.33329	0.18702
Planum temporale	Intercept	2144.95753	136.29575	15.73752	5.02916E-24
	Slope	10.25055	11.80269	0.86849	0.38827
Precuneus	Intercept	10113.7326	377.614	26.78326	3.57748E-37
	Slope	24.57816	32.69993	0.75163	0.45495

Fitted Curves Plot



Residual Plots

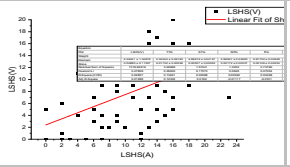


B5-3: FreeSurfer Correlation results for right hemisphere thickness with $LSHS_{(A)}$.

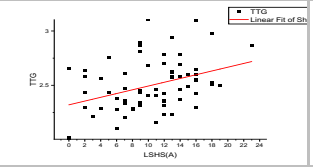
		Value	Standard Error	t-Value	Prob>|t|
LSHS(V)	Intercept	2.39341	1.32878	1.8012	0.07624
	Slope	0.50885	0.11507	4.42219	3.73521E-5
TTG	Intercept	2.32042	0.06193	37.46556	3.3641E-46
	Slope	0.01732	0.00536	3.22876	0.00194
STG	Intercept	2.86819	0.04197	68.33522	5.62835E-63
	Slope	0.00527	0.00363	1.45021	0.15174
MTG	Intercept	2.99567	0.03895	76.90569	2.54099E-66
	Slope	0.00172	0.00337	0.5096	0.61203
ITG	Intercept	2.87702	0.02928	98.24697	2.78772E-73
	Slope	0.00146	0.00254	0.57452	0.56757
Insula	Intercept	3.15162	0.04799	65.67491	7.45311E-62
	Slope	0.00304	0.00416	0.73151	0.46706
IFG	Intercept	2.62581	0.03871	67.82493	9.16775E-63
	Slope	0.00253	0.00335	0.75535	0.45273
MFG	Intercept	2.83515	0.03327	85.20497	3.13569E-69
	Slope	0.00184	0.00288	0.64003	0.52437
Fusiform	Intercept	2.80456	0.03144	89.20874	1.55317E-70
	Slope	0.00387	0.00272	1.42144	0.1599
Supramarginal	Intercept	2.6892	0.03606	74.58386	1.87885E-65
	Slope	0.00289	0.00312	0.92553	0.35806
Lingual	Intercept	2.10945	0.02917	72.30763	1.41825E-64
	Slope	0.00313	0.00253	1.24039	0.21922
Postcentral	Intercept	2.10151	0.03577	58.75698	1.02307E-58
	Slope	0.00572	0.0031	1.84682	0.06926
Planum temporale	Intercept	3.59761	0.11926	30.16516	2.50773E-40
	Slope	-0.01004	0.01033	-0.97207	0.33457
Precuneus	Intercept	2.45436	0.02886	85.03807	3.56484E-69
	Slope	0.00543	0.0025	2.1724	0.03342

Fitted Curves Plot

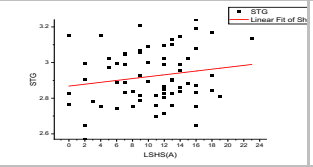
LSHS(V)



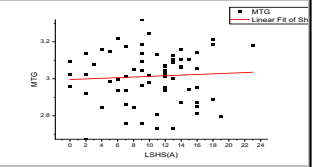
TTG



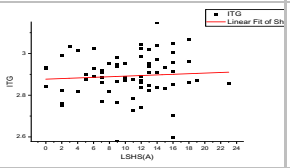
STG



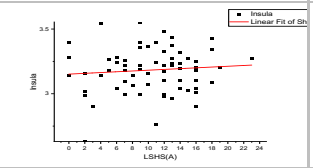
MTG



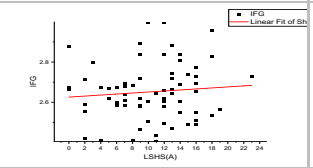
ITG



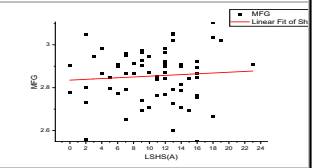
Insula



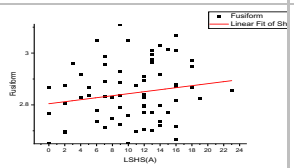
IFG



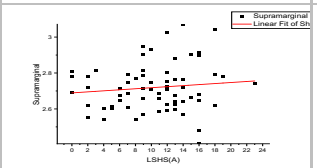
MFG



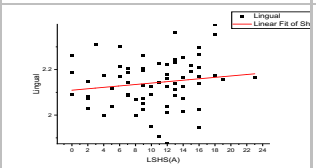
Fusiform



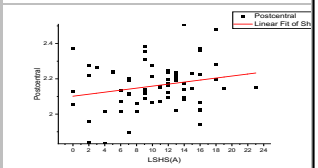
Supramarginal



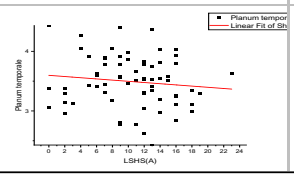
Lingual



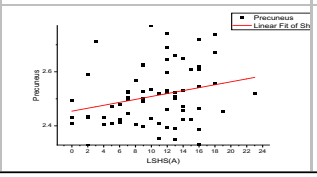
Postcentral



Planum temporale

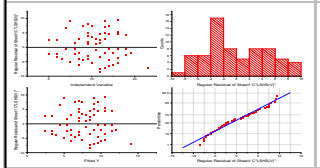


Precuneus

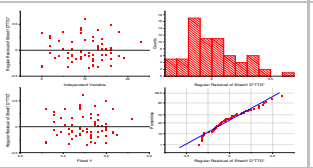


Residual Plots

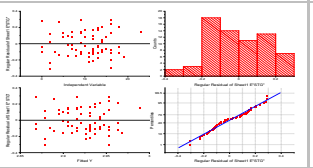
LSHS(V)



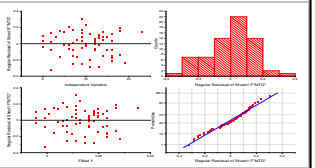
TTG



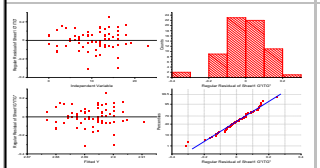
STG



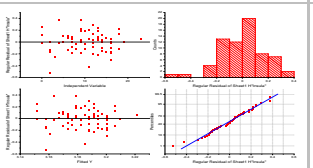
MTG



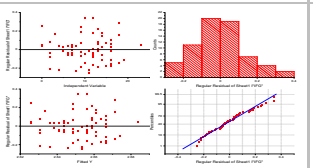
ITG



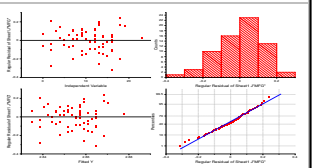
Insula



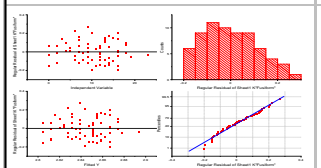
IFG



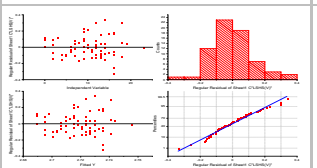
MFG



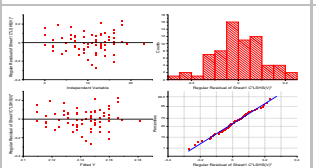
Fusiform



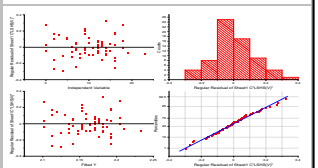
Supramarginal



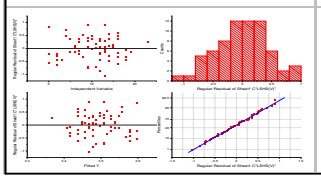
Lingual



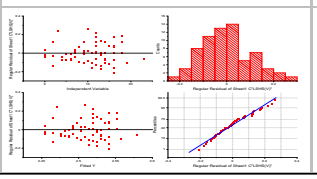
Postcentral



Planum temporale



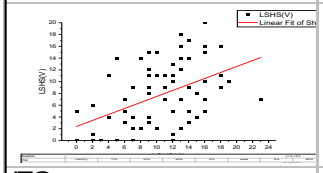
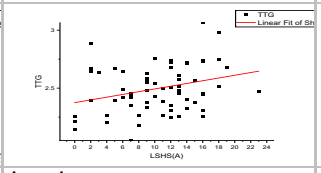
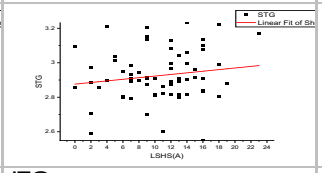
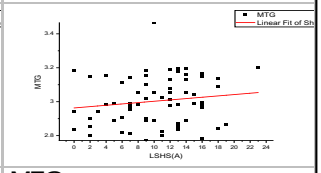
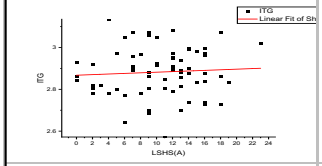
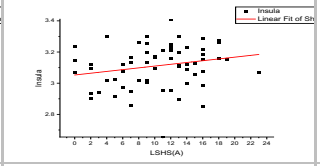
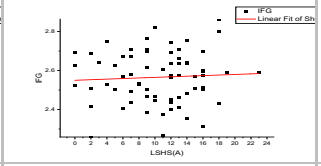
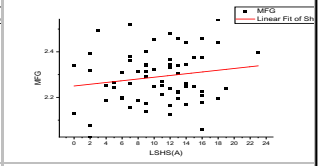
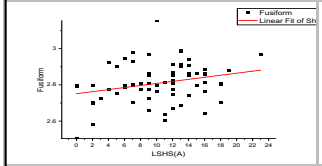
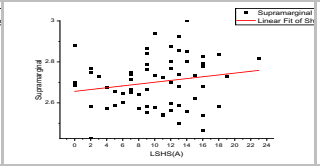
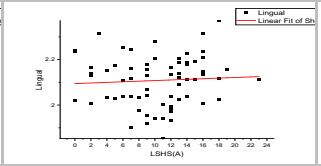
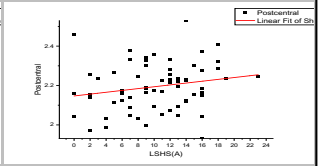
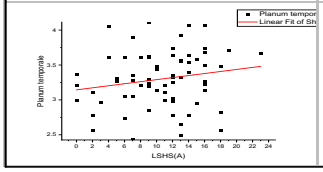
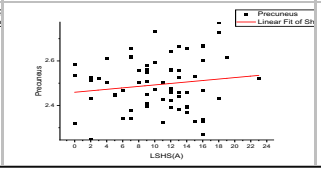
Precuneus



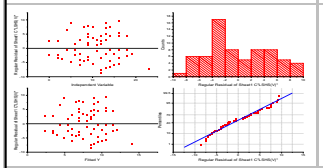
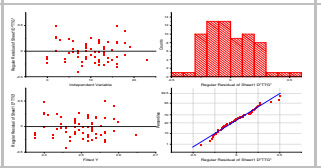
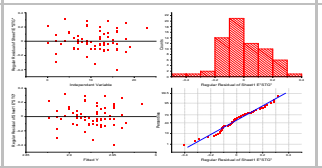
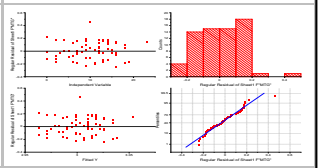
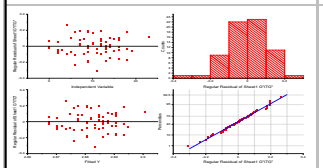
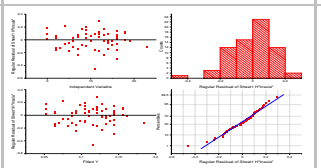
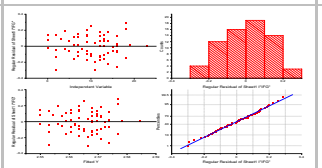
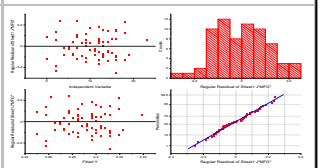
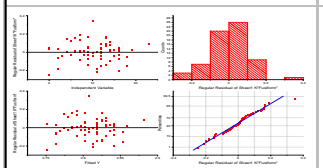
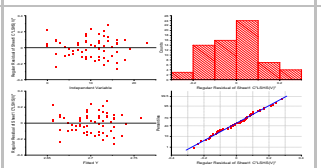
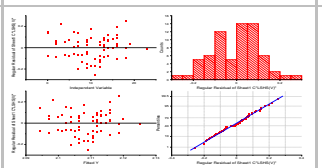
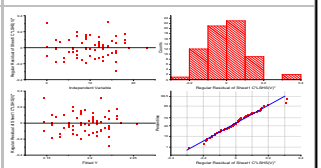
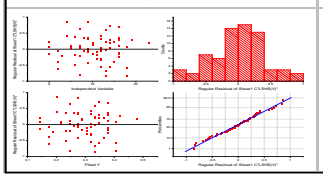
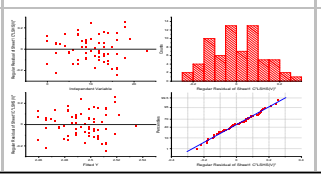
B5-4: FreeSurfer Correlation results for left hemisphere thickness with $LSHS_{(A)}$.

		Value	Standard Error	t-Value	Prob>|t|
LSHS(V)	Intercept	2.39341	1.32878	1.8012	0.07624
	Slope	0.50885	0.11507	4.42219	3.73521E-5
TTG	Intercept	2.37494	0.05418	43.83411	1.58079E-50
	Slope	0.01181	0.00469	2.51793	0.01424
STG	Intercept	2.87624	0.04028	71.39752	3.23832E-64
	Slope	0.00468	0.00349	1.34059	0.18465
MTG	Intercept	2.96307	0.03862	76.72665	2.95859E-66
	Slope	0.00394	0.00334	1.17958	0.2424
ITG	Intercept	2.86742	0.03202	89.54352	1.21538E-70
	Slope	0.00145	0.00277	0.52172	0.60361
Insula	Intercept	3.05256	0.03728	81.87117	4.26451E-68
	Slope	0.00573	0.00323	1.77354	0.08075
IFG	Intercept	2.54997	0.03684	69.20876	2.46161E-63
	Slope	0.0015	0.00319	0.46885	0.64072
MFG	Intercept	2.25	0.03126	71.97757	1.91108E-64
	Slope	0.00385	0.00271	1.42063	0.16013
Fusiform	Intercept	2.75136	0.02963	92.86561	1.11835E-71
	Slope	0.00565	0.00257	2.20035	0.03129
Supramarginal	Intercept	2.6561	0.0331	80.2385	1.59083E-67
	Slope	0.00445	0.00287	1.55324	0.12515
Lingual	Intercept	2.09439	0.03032	69.08759	2.75914E-63
	Slope	0.00134	0.00263	0.51066	0.61129
Postcentral	Intercept	2.14696	0.03227	66.52379	3.23303E-62
	Slope	0.00468	0.00279	1.67376	0.09891
Planum temporale	Intercept	3.14362	0.10889	28.86905	3.72138E-39
	Slope	0.01463	0.00943	1.55163	0.12553
Precuneus	Intercept	2.45925	0.03252	75.61903	7.64342E-66
	Slope	0.0033	0.00282	1.17071	0.24593

Fitted Curves Plot

LSHS(V)	TTG	STG	MTG
			
ITG	**Insula**	**IFG**	**MFG**
			
Fusiform	**Supramarginal**	**Lingual**	**Postcentral**
			
Planum temporale	**Precuneus**		
			

Residual Plots

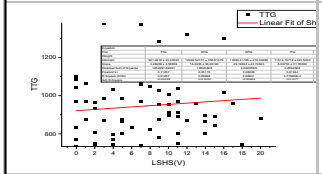
LSHS(V)	TTG	STG	MTG
			
ITG	**Insula**	**IFG**	**MFG**
			
Fusiform	**Supramarginal**	**Lingual**	**Postcentral**
			
Planum temporale	**Precuneus**		
			

B6-1: FreeSurfer Correlation results for right hemisphere volume with $LSHS_{(V)}$.

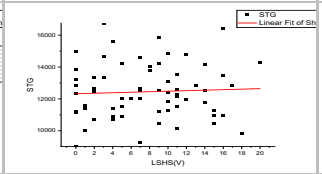
		Value	Standard Error	t-Value	Prob>|t|
TTG	Intercept	921.4918	33.43523	27.5605	6.30849E-38
	Slope	3.28268	3.56659	0.9204	0.36072
STG	Intercept	12322.52151	356.81379	34.53488	5.62117E-44
	Slope	16.0336	38.06193	0.42125	0.67494
MTG	Intercept	13090.41785	419.49488	31.20519	3.09323E-41
	Slope	29.19844	44.74823	0.6525	0.51634
ITG	Intercept	11510.70718	391.5093	29.40085	1.21532E-39
	Slope	6.59753	41.76296	0.15798	0.87496
Insula	Intercept	7459.6011	200.18769	37.26304	4.735E-46
	Slope	10.06346	21.35436	0.47126	0.63901
IFG	Intercept	15857.09895	439.2874	36.09732	3.50227E-45
	Slope	40.06565	46.85953	0.85502	0.39564
MFG	Intercept	23737.92485	674.25505	35.20615	1.68275E-44
	Slope	-33.73925	71.92392	-0.4691	0.64055
Fusiform	Intercept	10169.82173	301.9872	33.67633	2.71164E-43
	Slope	2.21671	32.21348	0.06881	0.94535
Supramarginal	Intercept	11460.62248	354.71465	32.30941	3.58107E-42
	Slope	-16.53128	37.83801	-0.4369	0.66361
Lingual	Intercept	7385.22331	244.60524	30.19242	2.372E-40
	Slope	30.71995	26.09245	1.17735	0.24328
Postcentral	Intercept	10014.35063	343.77002	29.13096	2.13991E-39
	Slope	-32.19127	36.67053	-0.87785	0.38321
Planum temporale	Intercept	2284.7463	94.16191	24.26402	1.34121E-34
	Slope	7.49857	10.04441	0.74654	0.45799
Precuneus	Intercept	10908.347	343.96849	31.71322	1.13773E-41
	Slope	-15.65631	36.6917	-0.4267	0.67099

Fitted Curves Plot

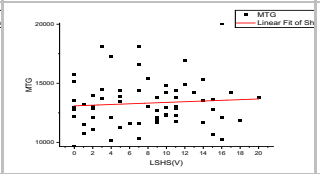
TTG



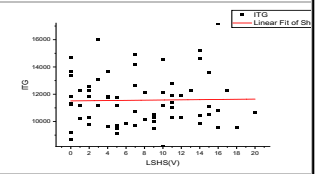
STG



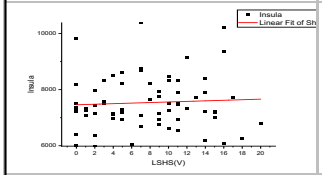
MTG



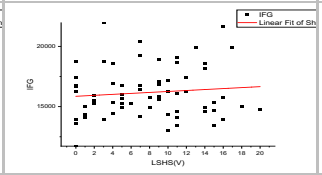
ITG



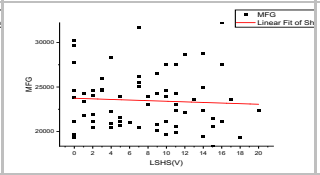
Insula



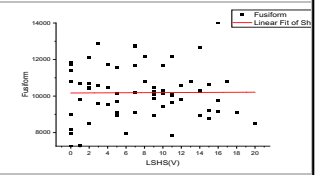
IFG



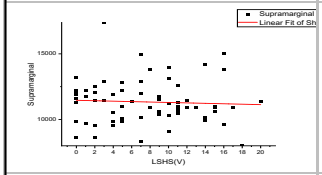
MFG



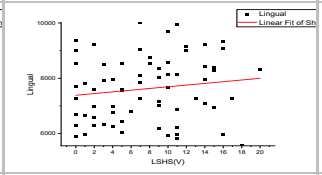
Fusiform



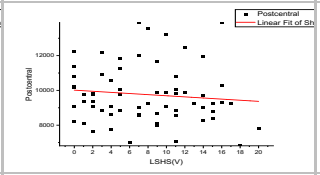
Supramarginal



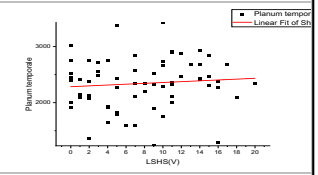
Lingual



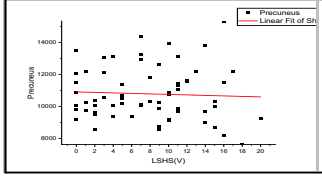
Postcentral



Planum temporale

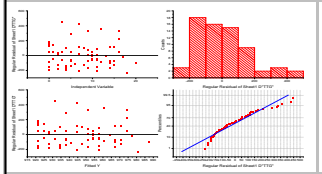


Precuneus

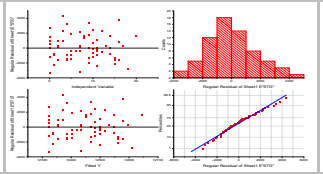


Residual Plots

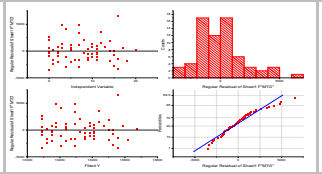
TTG



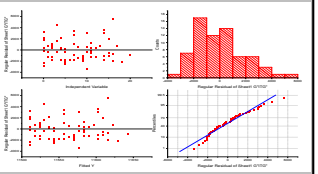
STG



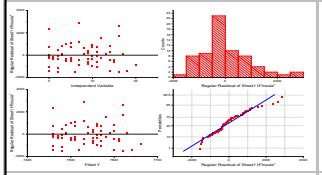
MTG



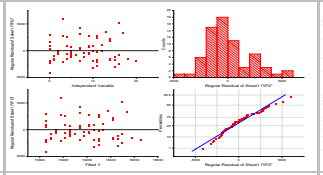
ITG



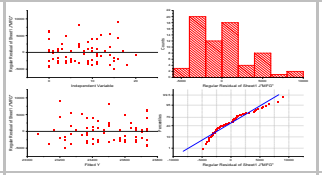
Insula



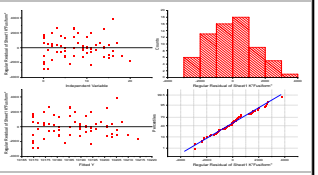
IFG



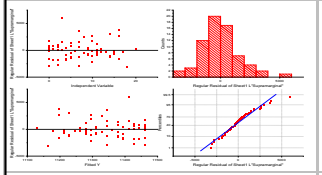
MFG



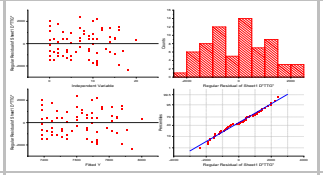
Fusiform



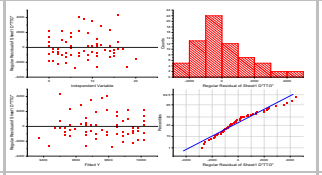
Supramarginal



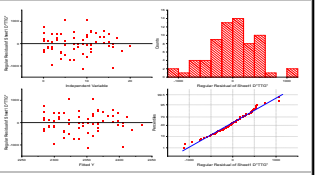
Lingual



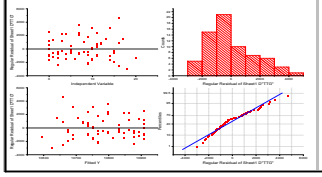
Postcentral



Planum temporale



Precuneus

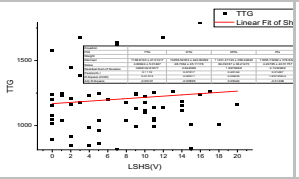


B6-2: FreeSurfer Correlation results for left hemisphere volume with $LSHS_{(V)}$.

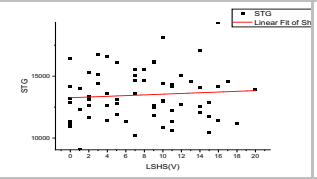
		Value	Standard Error	t-Value	Prob>|t|
TTG	Intercept	1168.8103	47.01317	24.86134	3.1489E-35
	Slope	4.80824	5.01497	0.95878	0.34117
STG	Intercept	13256.52353	422.90299	31.34649	2.33874E-41
	Slope	28.7364	45.11178	0.637	0.52633
MTG	Intercept	11401.47123	358.24622	31.8258	9.13292E-42
	Slope	84.09187	38.21473	2.20051	0.03128
ITG	Intercept	11855.73299	379.8343	31.21291	3.04627E-41
	Slope	4.23785	40.51757	0.10459	0.91702
Insula	Intercept	7413.16994	178.96042	41.42352	5.80951E-49
	Slope	12.1043	19.09001	0.63406	0.52823
IFG	Intercept	12995.17397	440.12677	29.52598	9.36344E-40
	Slope	17.23213	46.94906	0.36704	0.71476
MFG	Intercept	25329.72466	705.93303	35.8812	5.10807E-45
	Slope	-35.9967	75.30307	-0.47802	0.63421
Fusiform	Intercept	9970.74402	307.84901	32.38842	3.07678E-42
	Slope	38.76132	32.83877	1.18035	0.2421
Supramarginal	Intercept	12546.58282	451.68967	27.777	3.9191E-38
	Slope	-9.3901	48.1825	-0.19489	0.84608
Lingual	Intercept	7084.66738	244.9292	28.92537	3.30275E-39
	Slope	-5.55629	26.12701	-0.21266	0.83224
Postcentral	Intercept	10214.85951	304.41439	33.55577	3.39191E-43
	Slope	1.61217	32.4724	0.04965	0.96055
Planum temporale	Intercept	2135.82912	103.09643	20.71681	1.37465E-30
	Slope	15.05291	10.99747	1.36876	0.17571
Precuneus	Intercept	10297.73716	289.05035	35.6261	7.99605E-45
	Slope	9.27179	30.83349	0.30071	0.76458

Fitted Curves Plot

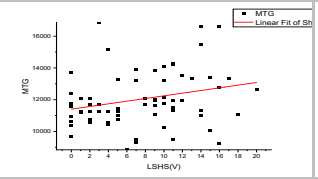
TTG



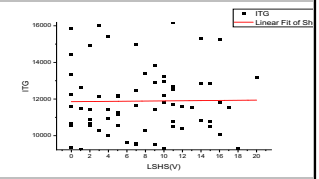
STG



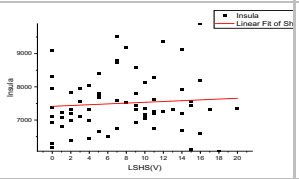
MTG



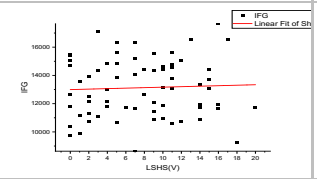
ITG



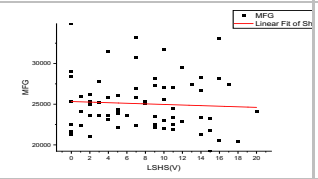
Insula



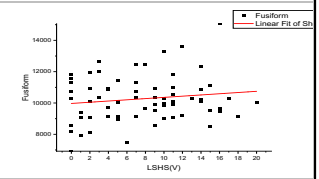
IFG



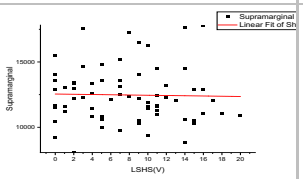
MFG



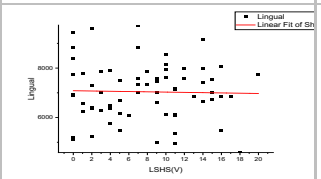
Fusiform



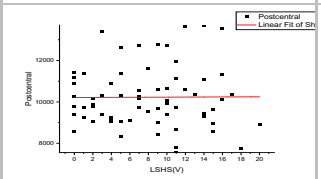
Supramarginal



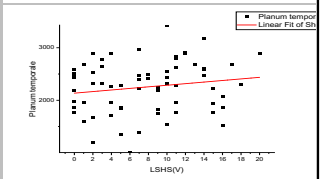
Lingual



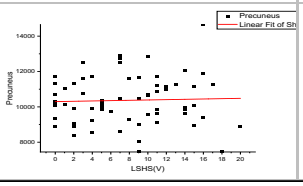
Postcentral



Planum temporale

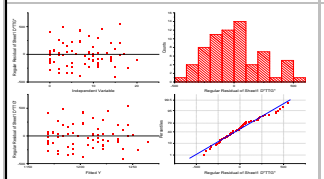


Precuneus

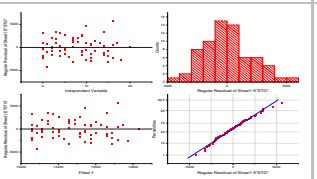


Residual Plots

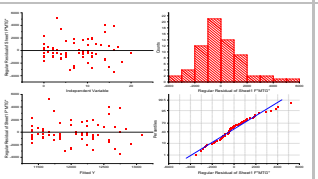
TTG



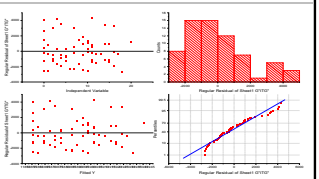
STG



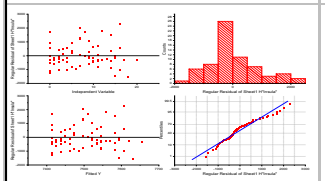
MTG



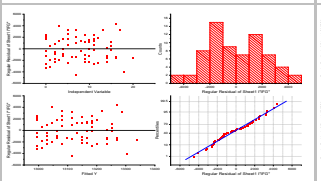
ITG



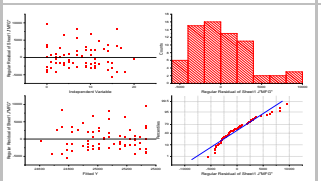
Insula



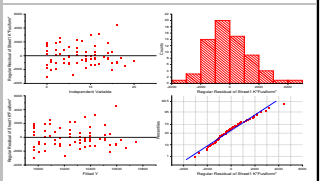
IFG



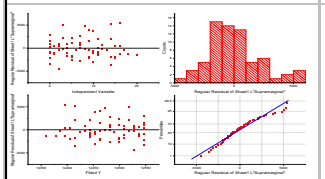
MFG



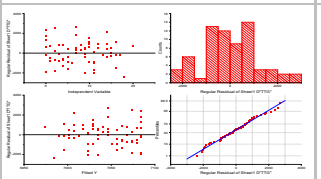
Fusiform



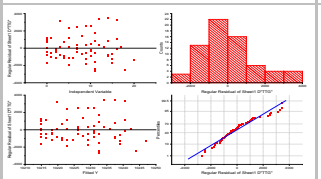
Supramarginal



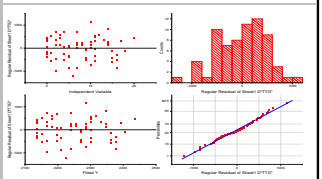
Lingual



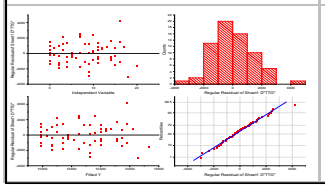
Postcentral



Planum temporale



Precuneus

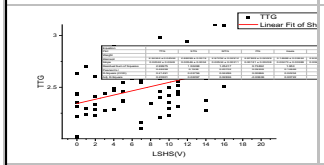


B6-3: FreeSurfer Correlation results for right hemisphere thickness with $LSHS_{(V)}$.

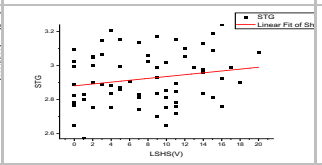
		Value	Standard Error	t-Value	Prob>|t|
TTG	Intercept	2.34344	0.04504	52.02857	2.64965E-55
	Slope	0.02042	0.0048	4.25048	6.85338E-5
STG	Intercept	2.88099	0.0319	90.30411	6.98535E-71
	Slope	0.00546	0.0034	1.60483	0.11331
MTG	Intercept	2.97252	0.02912	102.06493	2.28781E-74
	Slope	0.00534	0.00311	1.71912	0.09028
ITG	Intercept	2.87828	0.02229	129.10526	4.52553E-81
	Slope	0.00181	0.00238	0.75951	0.45025
Insula	Intercept	3.14688	0.03634	86.58859	1.09301E-69
	Slope	0.00473	0.00388	1.21958	0.22697
IFG	Intercept	2.63337	0.02952	89.19968	1.56353E-70
	Slope	0.00244	0.00315	0.77483	0.4412
MFG	Intercept	2.82205	0.02499	112.91627	3.01548E-77
	Slope	0.0042	0.00267	1.57563	0.11989
Fusiform	Intercept	2.80873	0.02373	118.34247	1.3816E-78
	Slope	0.00469	0.00253	1.85251	0.06843
Supramarginal	Intercept	2.71176	0.02766	98.05187	3.17578E-73
	Slope	9.69855E-4	0.00295	0.32875	0.74339
Lingual	Intercept	2.12382	0.02234	95.05527	2.4289E-72
	Slope	0.00237	0.00238	0.99299	0.32434
Postcentral	Intercept	2.16131	0.02798	77.25617	1.88834E-66
	Slope	-5.39721E-5	0.00298	-0.01809	0.98563
Planum temporale	Intercept	3.39383	0.09038	37.54869	2.92511E-46
	Slope	0.01297	0.00964	1.34512	0.18319
Precuneus	Intercept	2.4957	0.02267	110.06391	1.61798E-76
	Slope	0.00196	0.00242	0.80994	0.42088

Fitted Curves Plot

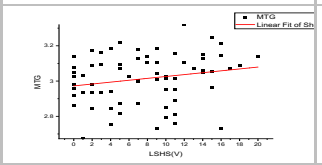
TTG



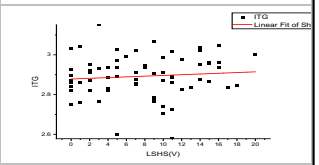
STG



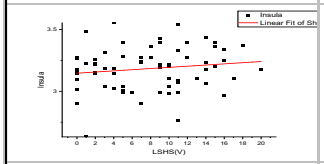
MTG



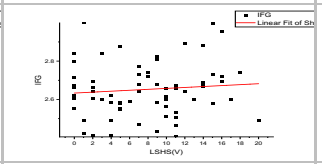
ITG



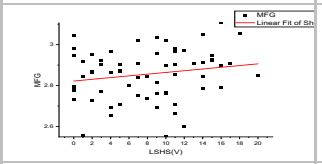
Insula



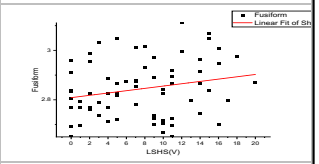
IFG



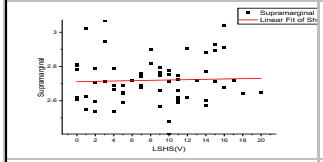
MFG



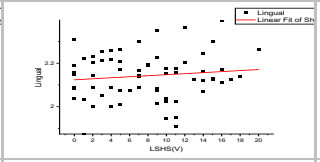
Fusiform



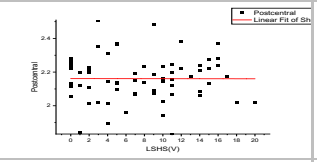
Supramarginal



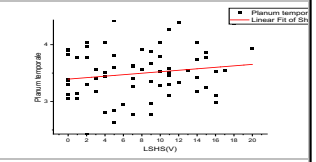
Lingual



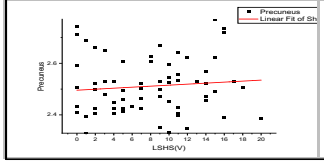
Postcentral



Planum temporale

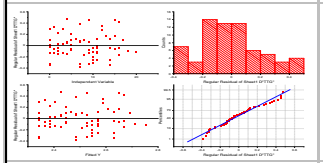


Precuneus

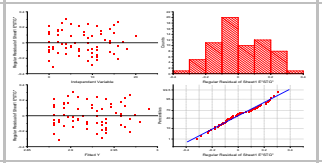


Residual Plots

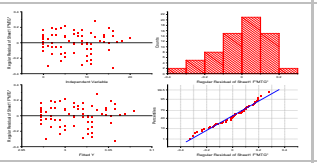
TTG



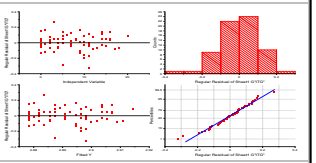
STG



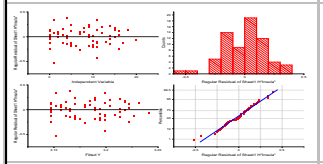
MTG



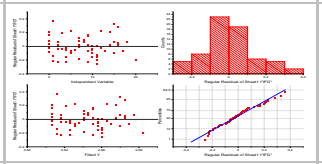
ITG



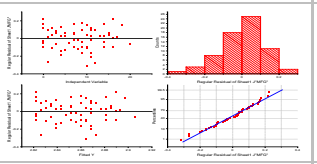
Insula



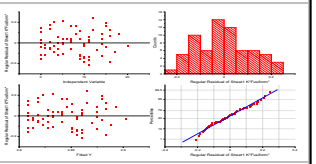
IFG



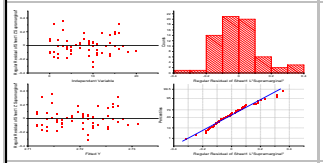
MFG



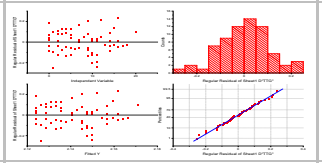
Fusiform



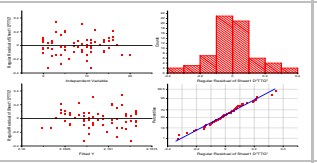
Supramarginal



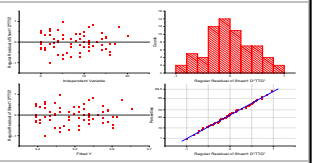
Lingual



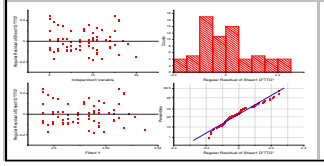
Postcentral



Planum temporale



Precuneus

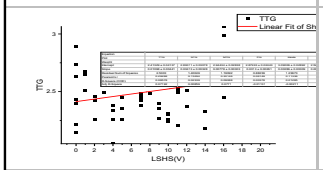


B6-4: FreeSurfer Correlation results for left hemisphere thickness with $LSHS_{(V)}$.

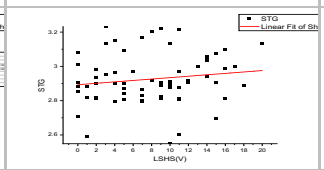
		Value	Standard Error	t-Value	Prob>|t|
TTG	Intercept	2.41329	0.04137	58.33853	1.62541E-58
	Slope	0.01098	0.00441	2.48846	0.01536
STG	Intercept	2.89311	0.03078	94.00623	5.02604E-72
	Slope	0.00413	0.00328	1.25726	0.21309
MTG	Intercept	2.94434	0.02838	103.74759	7.82607E-75
	Slope	0.00778	0.00303	2.56854	0.01248
ITG	Intercept	2.87243	0.02443	117.58425	2.10758E-78
	Slope	0.0013	0.00261	0.50047	0.61841
Insula	Intercept	3.09006	0.02892	106.84663	1.1343E-75
	Slope	0.00286	0.00309	0.92695	0.35733
IFG	Intercept	2.52978	0.02763	91.55113	2.84526E-71
	Slope	0.00465	0.00295	1.57871	0.11918
MFG	Intercept	2.27466	0.0241	94.40156	3.81773E-72
	Slope	0.00199	0.00257	0.77349	0.44199
Fusiform	Intercept	2.77544	0.02283	121.57445	2.35215E-79
	Slope	0.0045	0.00244	1.84734	0.06918
Supramarginal	Intercept	2.66682	0.02515	106.05535	1.84753E-75
	Slope	0.00463	0.00268	1.72426	0.08934
Lingual	Intercept	2.10263	0.02315	90.81808	4.81705E-71
	Slope	7.39401E-4	0.00247	0.29939	0.76558
Postcentral	Intercept	2.18198	0.02505	87.10342	7.41559E-70
	Slope	0.00177	0.00267	0.66062	0.51116
Planum temporale	Intercept	3.12995	0.08081	38.73185	4.12028E-47
	Slope	0.02157	0.00862	2.50225	0.01483
Precuneus	Intercept	2.47972	0.02498	99.28427	1.40016E-73
	Slope	0.00179	0.00266	0.67289	0.50337

Fitted Curves Plot

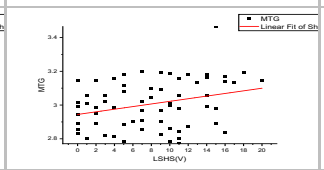
TTG



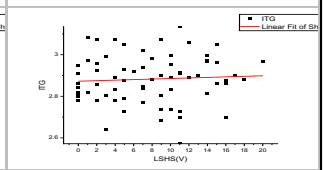
STG



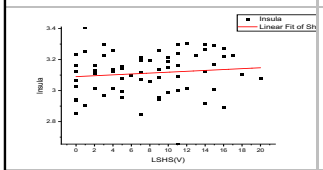
MTG



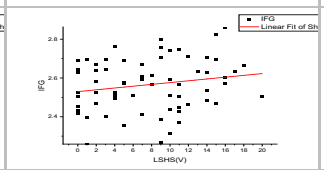
ITG



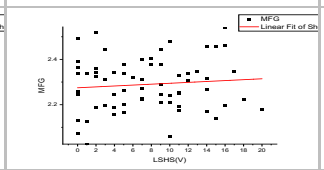
Insula



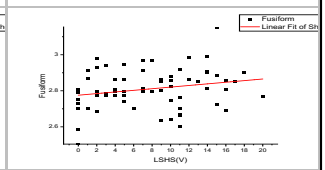
IFG



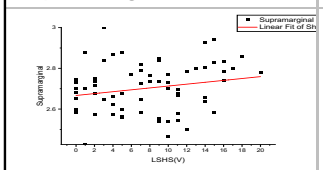
MFG



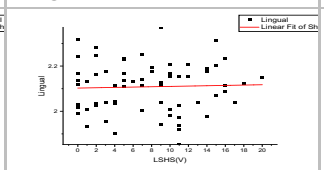
Fusiform



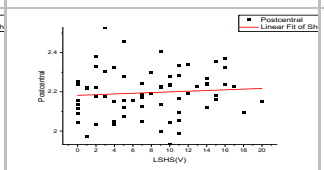
Supramarginal



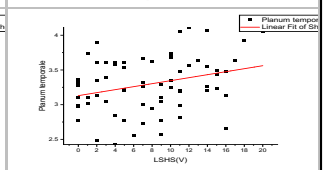
Lingual



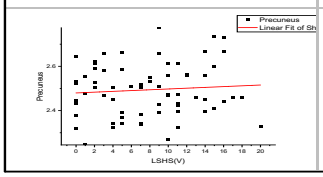
Postcentral



Planum temporale

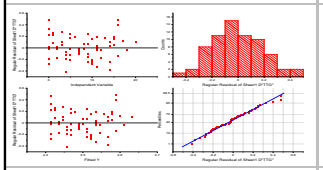


Precuneus

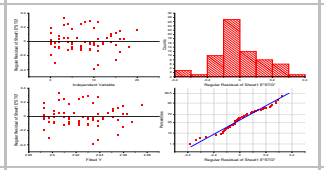


Residual Plots

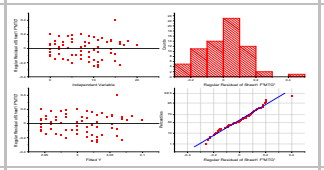
TTG



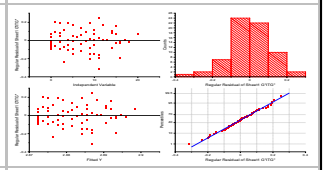
STG



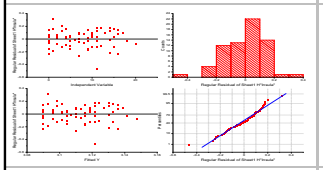
MTG



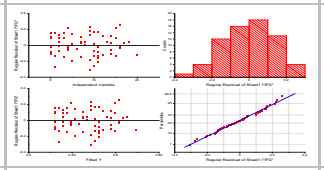
ITG



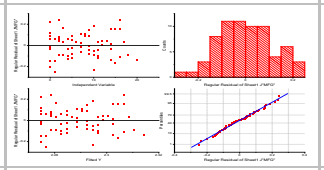
Insula



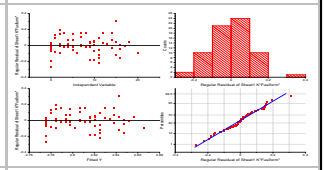
IFG



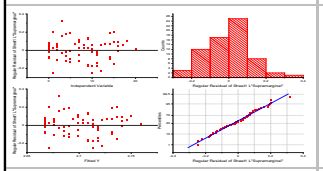
MFG



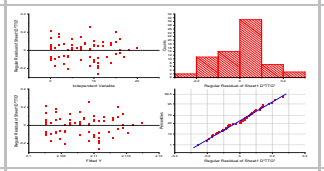
Fusiform



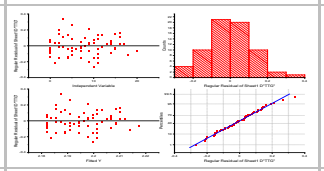
Supramarginal



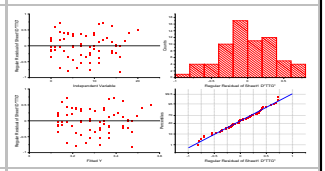
Lingual



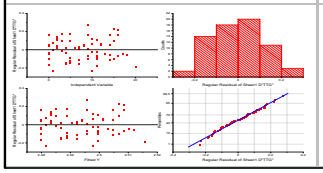
Postcentral



Planum temporale



Precuneus



Appendix C

C1-1: Voice block correlation with $LSHS_{(M)}$.

	RT-Cingulate	LT-cingulate	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-TTG	LT-TTG	RT-STG	LT-STG	RT-MTG	LT-MTG	RT-ITG	LT-ITG
r	-0.086	-0.03	0.07	0.14	0.01	0.03	0.1	0.01	0.03	0.09	0.05	0.07	0.15	0.03
P value	0.48	0.79	0.56	0.23	0.89	0.75	0.41	0.9	0.79	0.47	0.65	0.55	0.2	0.75

C1-2: Voice block correlation with $LSHS_{(A)}$.

	RT-Cingulate	LT-cingulate	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-TTG	LT-TTG	RT-STG	LT-STG	RT-MTG	LT-MTG	RT-ITG	LT-ITG
r	-0.15	-0.09	0.04	0.19	0.07	0.005	0.23	0.13	0.06	0.16	-0.05	0.11	0.2	0.05
P value	0.22	0.44	0.7	0.12	0.53	0.96	0.05	0.28	0.58	0.19	0.67	0.37	0.09	0.67

C1-3: Voice block correlation with $LSHS_{(V)}$.

	RT-Cingulate	LT-cingulate	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-TTG	LT-TTG	RT-STG	LT-STG	RT-MTG	LT-MTG	RT-ITG	LT-ITG
r	-0.08	0.01	0.05	0.19	0.04	0.04	0.001	0.02	0.08	0.27	0.11	0.12	0.22	0.01
P value	0.49	0.91	0.96	0.11	0.71	0.7	0.99	0.84	0.51	0.02	0.34	0.31	0.07	0.92

C2-1: Text block correlation with $LSHS_{(M)}$.

	RT-Cingulate	LT-cingulate	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-TTG	LT-TTG	RT-STG	LT-STG	RT-MTG	LT-MTG	RT-ITG	LT-ITG
r	-0.07	-0.06	0.04	0.011	0.09	0.08	0.02	0.01	0.01	0.02	0.05	0.03	0.18	0.06
P value	0.53	0.6	0.7	036	0.46	0.5	0.87	0.9	0.93	0.84	0.66	0.76	0.14	0.61

C2-2: Text block correlation with $LSHS_{(A)}$.

	RT-Cingulate	LT-cingulate	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-TTG	LT-TTG	RT-STG	LT-STG	RT-MTG	LT-MTG	RT-ITG	LT-ITG
r	-0.19	-0.17	0.08	0.02	0.21	-0.22	0.00002	0.02	0.03	0.11	0.11	0.09	0.07	0.07
P value	0.211	0.15	0.47	0.85	0.08	0.06	0.99	0.85	0.77	0.34	0.34	0.43	0.55	0.54

C2-3: Text block correlation with $LSHS_{(V)}$.

	RT-Cingulate	LT-cingulate	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-TTG	LT-TTG	RT-STG	LT-STG	RT-MTG	LT-MTG	RT-ITG	LT-ITG
r	0.01	0.009	0.08	0.18	0.06	0.04	-0.06	0.03	0.06	0.05	0.05	0.13	0.14	0.06
P value	0.91	0.94	0.47	0.13	0.6	0.69	0.62	0.76	0.61	0.63	0.63	0.27	0.22	0.6

C3-1: Faces task correlation with LSHS$_{(M)}$.

	RT-Fusiform	LT-Fusiform	RT-Amygdala	LT-Amygdala	RT-Precuneus	LT-Precuneus	RT-superior occipital	LT-superior occipital	RT-middle occipital	LT-middle occipital
r	0.03	0.08	-0.15	-0.04	0.13	0.12	0.12	0.17	0.12	0.2
P value	0.75	0.51	0.2	0.7	0.29	0.31	0.3	0.15	0.3	0.09

C3-2: Faces task correlation with LSHS$_{(A)}$.

	RT-Fusiform	LT-Fusiform	RT-Amygdala	LT-Amygdala	RT-Precuneus	LT-Precuneus	RT-superior occipital	LT-superior occipital	RT-middle occipital	LT-middle occipital
r	0.02	0.17	-0.18	-0.04	0.06	0.08	0.1	0.08	0.1	0.22
P value	0.84	0.15	0.14	0.7	0.6	0.5	0.39	0.47	0.38	0.06

C3-3: Faces task correlation with LSHS$_{(V)}$.

	RT-Fusiform	LT-Fusiform	RT-Amygdala	LT-Amygdala	RT-Precuneus	LT-Precuneus	RT-superior occipital	LT-superior occipital	RT-middle occipital	LT-middle occipital
r	-0.074	-0.078	-0.2	-0.13	0.07	0.1	0.09	0.11	0.04	0.05
P value	0.55	0.53	-0.1	0.27	0.54	0.38	0.43	0.37	0.69	0.63

C4-1: Audio/Visual task correlation with LSHS$_{(M)}$.

	RT-Fusiform	LT-Fusiform	RT-Amygdala	LT-Amygdala	RT-Precuneus	LT-Precuneus	RT-superior occipital	LT-superior occipital	RT-middle occipital	LT-middle occipital
r	0.02	0.02	0.06	0.15	0.1	0.12	0.16	0.12	0.07	0.16
P value	0.86	0.88	0.63	0.24	0.44	0.36	0.22	0.37	0.56	0.22

C4-2: Audio/Visual task correlation with LSHS$_{(A)}$.

	RT-Fusiform	LT-Fusiform	RT-Amygdala	LT-Amygdala	RT-Precuneus	LT-Precuneus	RT-superior occipital	LT-superior occipital	RT-middle occipital	LT-middle occipital
r	-0.2	-0.2	-0.17	-0.12	0.19	0.15	0.11	0.13	0.13	0.07
P value	0.06	0.07	0.2	0.34	0.15	0.26	0.39	0.3	0.32	0.6

C4-3: Audio/Visual task correlation with LSHS$_{(V)}$.

	RT-Fusiform	LT-Fusiform	RT-Amygdala	LT-Amygdala	RT-Precuneus	LT-Precuneus	RT-superior occipital	LT-superior occipital	RT-middle occipital	LT-middle occipital
r	0.03	0.04	0.03	0.12	0.13	0.14	0.23	0.19	0.12	0.18

P value	0.79	0.7	0.8	0.38	0.31	0.28	0.08	0.15	0.35	0.17

C5-1: Inhibition-Faces task language areas activation correlation with $LSHS_{(M)}$.

	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-MTG	LT-MTG	RT-STG	LT-STG	RT-TTG	LT-TTG
r	0.04	0.04	0.02	0.11	-0.01	0.11	0.1	0.03	-0.06	-0.02
P value	0.71	0.69	0.86	0.37	0.87	0.37	0.4	0.75	0.59	0.85

C5-2: Inhibition-Faces task language areas activation correlation with $LSHS_{(A)}$.

	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-MTG	LT-MTG	RT-STG	LT-STG	RT-TTG	LT-TTG
r	0.03	-0.04	0.11	0.12	0.02	0.12	0.13	0.09	0.05	0.09
P value	0.78	0.71	0.35	0.33	0.82	0.33	0.28	0.44	0.64	0.45

C5-3: Inhibition-Faces task language areas activation correlation with $LSHS_{(V)}$.

	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-MTG	LT-MTG	RT-STG	LT-STG	RT-TTG	LT-TTG
r	0.16	0.17	0.1	0.2	0.04	0.2	0.24	0.14	0.02	0.05
P value	0.19	0.16	0.39	0.09	0.71	0.09	0.04*	0.24	0.84	0.65

C6-1:Inhibition-audio/visual task language areas activation correlation with $LSHS_{(M)}$.

	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-MTG	LT-MTG	RT-STG	LT-STG	RT-TTG	LT-TTG
r	0.01	-0.19	0.04	0.07	0.02	0.07	0.05	0.08	0.007	0.09
P value	0.89	0.15	0.74	0.57	0.86	0.57	0.66	0.56	0.95	0.5

C6-2: Inhibition- audio/visual task language areas activation correlation with $LSHS_{(A)}$.

	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-MTG	LT-MTG	RT-STG	LT-STG	RT-TTG	LT-TTG
r	0.27	0.08	0.2	0.02	0.29	0.13	0.31	0.18	0.2	0.16
P value	0.04*	0.54	0.13	0.83	0.02*	0.31	0.01*	0.17	0.14	0.22

C6-3: Inhibition- audio/visual task language areas activation correlation with $LSHS_{(V)}$.

	RT-IFG	LT-IFG	RT-MFG	LT-MFG	RT-MTG	LT-MTG	RT-STG	LT-STG	RT-TTG	LT-TTG
r	0.04	-0.15	0.1	0.009	0.01	0.05	0.09	-0.03	0.05	0.03
P value	0.76	0.27	0.43	0.94	0.91	0.68	00.48	0.79	0.7	0.78

C7-1: Voice Block Lateralization index (LI) correlation with $LSHS_{(M)}$.

	Cingulate	Fusiform	Insula	IFG	SFG	MFG	MTG	TTG	STG	ITG
r	0.006	0.01	0.01	0.03	0.04	0.13	0.12	0.21	0.02	0.08
P value	0.96	0.9	0.91	0.75	0.72	0.27	0.31	0.09	0.87	0.5

C7-2 Voice Block Lateralization index (LI) correlation with $LSHS_{(A)}$.

	Cingulate	Fusiform	Insula	IFG	SFG	MFG	MTG	TTG	STG	ITG
r	0.03	-0.02	0.01	0.12	0.11	0.18	0.01	0.13	0.05	0.13
P value	0.75	0.83	0.92	0.31	0.34	0.12	0.88	0.27	0.67	0.26

C7-3 Voice Block Lateralization index (LI) correlation with $LSHS_{(V)}$.

	Cingulate	Fusiform	Insula	IFG	SFG	MFG	MTG	TTG	STG	ITG
r	0.02	0.01	0.08	0.12	0.17	0.18	0.09	0.12	0.16	0.17
P value	0.86	0.9	0.49	0.32	0.15	0.14	0.46	0.32	0.18	0.16

C8-1: Text Block Lateralization index (LI) correlation with $LSHS_{(M)}$.

	Cingulate	Fusiform	Insula	IFG	SFG	MFG	MTG	TTG	STG	ITG
r	0.03	-0.04	-0.02	0.11	0.1	0.00001	0.12	-0.01	0.1	-0.04
P value	0.8	0.72	0.82	0.36	0.4	0.9	0.3	0.93	0.41	0.74

C8-2: Text Block Lateralization index (LI) correlation with $LSHS_{(A)}$.

	Cingulate	Fusiform	Insula	IFG	SFG	MFG	MTG	TTG	STG	ITG
r	0.04	-0.02	-0.12	0.11	0.08	-0.02	0.08	-0.03	0.03	-0.01
P value	0.9	0.84	0.32	0.37	0.51	0.84	0.49	0.75	0.78	0.87

C8-3: Text Block Lateralization index (LI) correlation with $LSHS_{(V)}$.

	Cingulate	Fusiform	Insula	IFG	SFG	MFG	MTG	TTG	STG	ITG
r	0.02	-0.007	0.13	0.19	0.18	0.03	0.18	0.12	0.22	-0.009
P value	0.84	0.95	0.28	0.11	0.14	0.76	0.13	0.32	0.07	0.93